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### Defining the clinical phenotype of Saul-Wilson syndrome

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# Genetics in Medicine

## Defining the clinical phenotype of Saul-Wilson syndrome.

--Manuscript Draft--

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<b>Abstract:</b>	<p><b>Purpose:</b> Four patients with Saul-Wilson syndrome were reported between 1982 and 1994, but no additional individuals were described until 2018, when the molecular etiology of the disease was elucidated. Hence, the clinical phenotype of the disease remains poorly defined. We address this shortcoming by providing a detailed characterization of its phenotype.</p> <p><b>Methods:</b> Retrospective chart reviews were performed and primary radiographs assessed for all 14 individuals. Four individuals underwent detailed ophthalmologic examination by the same physician. Two individuals underwent gynecologic evaluation. Z-scores for height, weight, head circumference and BMI were calculated at different ages.</p> <p><b>Results:</b> All patients exhibited short stature, with sharp decline from the mean within the first months of life, and a final height Z-score between -4 and -8.5 standard deviations. The facial and radiographic features evolved over time. Intermittent neutropenia was frequently observed. Novel findings included elevation of liver transaminases, skeletal fragility, rod-cone dystrophy, and cystic macular changes.</p> <p><b>Conclusion:</b> Saul-Wilson syndrome presents a remarkably uniform phenotype, and the comprehensive description of our cohort allows for improved understanding of the long-term morbidity of the condition, establishment of follow-up recommendations for affected individuals, and documentation of the natural history into adulthood for comparison with treated patients, when therapeutics become available.</p>

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November 21, 2019

Robert D. Steiner, MD  
Editor-in-Chief  
*Genetics in Medicine*

Dear Dr. Steiner,

Please consider the enclosed manuscript, "Defining the clinical phenotype of Saul-Wilson syndrome", for publication in *Genetics in Medicine*.

Saul-Wilson syndrome is a rare skeletal dysplasia, first reported in 1982. Between then and 2018, only four patients were reported. Recently, we identified the molecular etiology of the disease. However, a detailed clinical characterization of the disease is still lacking. Here, we address this shortcoming by performing comprehensive phenotyping of 14 patients with Saul-Wilson syndrome, including long-term follow-up of two of the patients originally reported in the 1990s. We also describe novel findings, including rod-cone dystrophy, macular cystic changes, elevation of hepatic transaminases, bone fragility, and the intermittent pattern of neutropenia in Saul-Wilson syndrome. This disease is likely underdiagnosed; since the publication of our molecular paper one year ago, we have learned of several new cases diagnosed around the world. Since the current submission will represent the only publication with careful delineation of the clinical findings and recommendations for management, it will likely serve to call attention to this poorly known though likely underrecognized disorder.

We suggest Dr. V. Reid Sutton as the editor for our paper, given his expertise in the field of skeletal dysplasias. Recommended reviewers include Dr. Robert A. Saul at Greenville Health System ([RSaul@ghs.org](mailto:RSaul@ghs.org)), Dr. Roberta A. Pagon at University of Washington ([bpagon@uw.edu](mailto:bpagon@uw.edu)), and Dr. Joseph H. Hersh at University of Louisville ([jhhers01@louisville.edu](mailto:jhhers01@louisville.edu)). Dr. Saul described the original proband with Saul-Wilson syndrome back in 1982, and a subsequent follow-up of his patient in 1990 (PMID 2309787). Dr. Pagon diagnosed a patient in the 1990s (subject P7.1 in our cohort), and followed her for many years. Dr. Hersh reported a patient in 1994 (PMID 8074143,



subject P2.1 in our cohort) that he followed on an annual basis for many years. Thus, the three recommended reviewers are some of the few doctors in the world with experience in the long-term follow-up of Saul-Wilson syndrome.

This work has not been previously published elsewhere and is entirely novel. It is not under consideration at any other journal. Please feel free to contact me if you require any additional information.

Thank you for your consideration.

Sincerely,

A handwritten signature in black ink, appearing to read "Carlos Ferreira", is located below the "Sincerely," text.

Carlos Ferreira, MD, FACMG



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December 16, 2019

Robert D. Steiner, MD  
Editor-in-Chief  
*Genetics in Medicine*

Dear Dr. Steiner,

Thank you for editing our manuscript, and for finding it acceptable for publication pending final files. We now uploaded all figures in TIFF or PDF format, and moved the supplemental legends to a separate online-only supplemental file. The color artwork form, license to publish, and reporting checklist were previously uploaded.

Please do not hesitate to contact me if any further edits are required.

Kindest regards,

A handwritten signature in black ink, appearing to read "Carlos Ferreira", is located below the text "Kindest regards,".

Carlos Ferreira, MD, FACMG

## **Defining the clinical phenotype of Saul-Wilson syndrome.**

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## **ABSTRACT**

**Purpose:** Four patients with Saul-Wilson syndrome were reported between 1982 and 1994, but no additional individuals were described until 2018, when the molecular etiology of the disease was elucidated. Hence, the clinical phenotype of the disease remains poorly defined. We address this shortcoming by providing a detailed characterization of its phenotype.

**Methods:** Retrospective chart reviews were performed and primary radiographs assessed for all 14 individuals. Four individuals underwent detailed ophthalmologic examination by the same physician. Two individuals underwent gynecologic evaluation. Z-scores for height, weight, head circumference and BMI were calculated at different ages.

**Results:** All patients exhibited short stature, with sharp decline from the mean within the first months of life, and a final height Z-score between -4 and -8.5 standard deviations. The facial and radiographic features evolved over time. Intermittent neutropenia was frequently observed. Novel findings included elevation of liver transaminases, skeletal fragility, rod-cone dystrophy, and cystic macular changes.

**Conclusion:** Saul-Wilson syndrome presents a remarkably uniform phenotype, and the comprehensive description of our cohort allows for improved understanding of the long-term morbidity of the condition, establishment of follow-up recommendations for affected individuals, and documentation of the natural history into adulthood for comparison with treated patients, when therapeutics become available.

**Key Words:** Saul-Wilson syndrome; phenotype; COG4; G516R.

## INTRODUCTION

Saul-Wilson syndrome is a rare skeletal dysplasia originally described in 1982 in a child with bulging fontanelles, left clubfoot, severe short stature, blue sclerae, bilateral cataracts, blunted fingertips, and frequent otitis media with hearing loss.<sup>1</sup> In 1990, an update was provided on the original proband, and a second patient with similar features was reported,<sup>2,3</sup> while two additional affected individuals were described in 1994.<sup>4</sup> Recently, a recurrent *de novo* heterozygous COG4 amino acid substitution (p.Gly516Arg) was identified in 14 patients with the disease, including two of the four original individuals described in the 1990s.<sup>5</sup> COG4 is a component of the Conserved Oligomeric Golgi (COG) complex, a hetero-octameric protein complex that regulates vesicular trafficking between the Golgi apparatus and the endoplasmic reticulum (ER). Patients' fibroblasts demonstrated accelerated retrograde Golgi-to-ER vesicular trafficking, while at the same time showing delayed anterograde ER-to-Golgi trafficking, leading to disruption of the Golgi apparatus, with decreased volume and stack collapse. The glycosylation of a secreted proteoglycan, which normally takes place in the Golgi apparatus, was found to be impaired.<sup>5</sup>

Although the aforementioned work provides insight into the pathophysiology of the disease, a comprehensive clinical characterization of the phenotype is still needed. Our present work attempts to address this knowledge gap, as we provide an extensive description of the clinical phenotype of Saul-Wilson syndrome.

## METHODS

## ***Subjects***

P1.1 was enrolled in protocol 15-HG-0130, “Clinical and Genetic Evaluation of Individuals with Undiagnosed Disorders Through the Undiagnosed Diseases Network” (NCT02450851).<sup>6–8</sup> P1.1, P2.1, P7.1 and P10.1 were enrolled in 14-HG-0071 “Clinical and Basic Investigations into Known and Suspected Congenital Disorders of Glycosylation” (NCT02089789). P3.1, P4.1, P5.1, P6.1, P9.1, P10.1, P11.1, P12.1 and P13.1 were enrolled in protocol 76-HG-0238, “Diagnosis and Treatment of Patients with Inborn Errors of Metabolism or other Genetic Disorders” (NCT00369421). The aforementioned protocols were approved by the National Human Genome Research Institute (NHGRI) Institutional Review Board (IRB). P3.1, P4.1 and P8.1 were enrolled in protocol “Enquiry of Participation in a Research Project about Clinical and Molecular Studies on Rare Congenital Skeletal Disorders”, approved by the IRB of the Karolinska Institute in Sweden (2014/983-31/1). P2.1, P5.1, P5.2 and P7.1 were enrolled in the Primordial Registry at Nemours/Alfred I. duPont Hospital for Children, approved by the Nemours IRB. Written informed consent was obtained from all affected individuals or their parents/legal guardians; consent was also obtained for publication of patient photos, where appropriate. All 14 individuals were presented in a prior publication, focused on the molecular characterization of the disease.<sup>5</sup>

## ***Data collection***

Clinical and laboratory data were abstracted from the medical records by retrospective chart review. Further data were collected by direct interaction with participating

individuals or their parents. Radiographic images were reviewed for all patients.

### ***Ophthalmologic evaluation***

Comprehensive age-appropriate eye evaluations were performed on four patients who visited the NIH Clinical Center. These included an evaluation of visual acuity, color vision, stereopsis, ocular motility assessment, mapping of visual fields with MonCV kinetic perimetry (Metrovision, P renchies, France), measurement of axial length (IOLMaster, Carl Zeiss Meditec, Dublin, CA), slit-lamp microscopy, dilated fundus exam, and retinoscopy to assess refractive error. Part of this assessment was performed at a sedated eye exam for P1.1. Ancillary testing, when visit time and patient cooperation level allowed, included electroretinography with a UTAS console (LKC Technologies, Gaithersburg, MD) and Burian-Allen bipolar contact lens electrodes (Hansen Labs, Coralville, IA), color fundus photography (CFP) and fundus autofluorescence (FAF) imaging with Topcon (Topcon Medical Systems, Oakland, NJ), RetCAM3 (Clarity Medical System Inc., Pleasanton, CA), or Optos (Optos, Dumfermline, Scotland, UK) imaging systems, and Optical Coherence Tomography utilizing a Cirrus HD-OCT machine (Carl Zeiss Meditec, Dublin, CA).

### ***Gynecologic evaluation***

P2.1 and P7.1 underwent gynecologic evaluation through review of history and hormone testing for both patients and pelvic exam and pelvic ultrasound for one patient.

### ***Growth***

Growth data was available for 13 affected individuals. Growth parameters were corrected for gestational age. Individual growth parameters (height, weight, head circumference, and body mass index) were calculated at age groups selected *a priori*, as follows: birth, 3 months, 6 months, 9 months, 12 months, 18 months, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years and 8 years. Subsequently, mean, median, standard deviations, and Z-scores were calculated according to WHO<sup>9,10</sup> and UK90<sup>11–13</sup> references. For a graphic comparison of length/height to achondroplasia, stature reference from a European cohort was used.<sup>14</sup>

## RESULTS

Clinical summaries for all patients are provided in the Supplementary Materials, Appendix 1.

### ***Dysmorphic features***

The characteristic facial features are depicted in figure 1 and supplementary figure S1. During early infancy, patients have progeroid features that disappear within the first few months of life. Blue sclerae are also seen in early infancy, and can persist for several months. The scalp veins become particularly prominent in late infancy and during the toddler years. The columella becomes prominent during the first few years of life. In late childhood, the shape of the forehead, which was round in early childhood, becomes taller and less round. Short distal phalanges of the fingers and toes of variable severity are seen in all, regardless of age.

### ***Ocular manifestations***

The ocular manifestations of the four patients (P1.1, P2.1, P7.1 and P10.1) with comprehensive eye exams performed at the NIH Ophthalmic Genetics clinic are summarized in supplementary table S1 and documented in figure 2. All four had lamellar cataracts or a history of cataract extraction (with childhood-onset cataract). In addition, several whose ophthalmic histories were reviewed had progression of lamellar cataracts requiring surgical intervention in early adulthood. Nystagmus was present in two of the four individuals who visited the NIH Clinical Center. The underlying cause is difficult to ascertain but is likely multifactorial with a central element. Two of the four individuals examined at the NIH Ophthalmic Genetics clinic had small eyes with short axial length. Hyperopic refractive error was noted for these two patients as expected for short axial length; the other two had axial length within the normal range and were mildly myopic. A pigmentary retinopathy consistent with a rod-cone dystrophy was noted in all four patients, whereas macular cystic changes were documented in two of the four individuals seen at the NIH Clinical Center. Symptoms in this cohort include delayed dark adaptation, difficulty with night vision, and visual field deficits. Color vision can be affected with macular involvement. Although limited, our data indicated a trend towards progressively worse disease in older individuals; those specifically questioned indicated worsening of their night and peripheral vision with advancing age.

### ***Gynecologic findings***

Pubertal development was normal in both individuals (P2.1 and P7.1) undergoing gynecologic evaluation and age at menarche (12 years and 11.5 years) was similar to

that of the general population.<sup>15</sup> Both began hormonal treatment (oral contraceptive pills or contraceptive patch) at age 16-17 years, one to manage menorrhagia and severe dysmenorrhea and the other to regulate her cycles and suppress ovarian cysts. One experienced elevated blood pressure on hormonal treatment, prompting discontinued use after 1 year. One underwent pelvic examination and pelvic ultrasound, which showed a normal-appearing uterus and ovaries that were small but likely proportionate to stature. Hormone levels (FSH, LH, estradiol, testosterone, prolactin) were in the expected ranges for reproductive-age women. Though neither of the two adult females who underwent gynecologic evaluation has tried to conceive, regular menstrual cycles and a normal hormone profile suggest no impairment of the ability to conceive.

### ***Growth***

Table S2 demonstrates length/height, weight, head circumference, and body mass index as measured by standard deviation scores (corrected for gestational age) compared to the general population. Data is presented for individual patients, as well as mean and median for all available patients for the first eight years of life. Figure 3 presents standard deviation scores for length/height of individual patients compared to the general population; similar to what occurs in achondroplasia, there is a sharp decline in standard deviation scores during the first few months of life, with a final height between -4 to -8.5 SD scores.

### ***Skeletal findings***

Representative skeletal features are presented in Figure 4 and supplementary figure



S2. Hypoplasia of the odontoid process, overtubulation of long bones with diaphyseal narrowing and metaphyseal flaring, and megaepiphyses are universal findings. Oval lucencies of the proximal femora are found during infancy. The vertebral bodies are initially flat, but become taller with age. The vertebral endplates become more irregular with age. Squared-off, ivory epiphyses of the hands are seen in later childhood. Several individuals had fractures (4/14, see supplementary figure S3), in at least one case without any known trauma, and in other cases after minimal trauma. In addition, one had nonunion after surgical osteotomy (supplementary figure S4). Premature degenerative joint disease was seen in two adults in their 20s, with early joint replacement in one (see supplementary figure S2J).

### ***Laboratory findings***

Asymptomatic elevation of transaminases was noticed in several individuals (see supplementary figure S5), without abnormalities in other liver function indices. Aspartate aminotransferase (AST) was elevated more often than alanine aminotransferase (ALT). Although neutropenia was not appreciated in any person when blood counts were obtained within the first two months of life (n=4), it was noted in all individuals for whom values were available for analysis (n=12). This neutropenia was intermittent, but did not have any noticeable cyclic periodicity. One (P10.1) was receiving chronic granulocyte colony stimulating factor (G-CSF) prophylaxis, with reported improvement of counts. Response to G-CSF in P13.1 was seen during an episode of orbital cellulitis, with a baseline absolute neutrophil count (ANC) of 1080 cells/ $\mu$ L, which improved to 1950 cells/ $\mu$ L after three daily doses of G-CSF at 5 mcg/kg/dose.

## ***Misdiagnoses***

Frequent misdiagnoses included Wiedemann-Rautenstrauch syndrome (with overlapping findings of early progeroid features, poor growth, frontal prominence with persistent opening of the anterior fontanelle, prominent scalp veins, a convex nasal ridge and thin vermillion of the upper lip), Russell-Silver syndrome (considering the short stature, largely of prenatal onset with absence of postnatal catch-up growth, relative macrocephaly, large open fontanelle, blue sclerae, and ivory epiphyses), Hallermann-Streiff syndrome (given the short stature, cataracts, micrognathia, prominent scalp veins and slender diaphyses), pycnodysostosis (given the short stature, persistently open fontanelle, short distal phalanges, and nonunion), osteogenesis imperfecta (due to blue sclerae, bone fragility and hearing loss), and microcephalic osteodysplastic primordial dwarfism type II (due to profound short stature in most cases of prenatal onset, microcephaly, low hanging columella, thin bones with metaphyseal widening, metacarpal pseudoepiphyses, and ivory phalangeal epiphyses).

A summary of the most common clinical and imaging findings is presented in Figure 5.

## **DISCUSSION**

Several age-dependent findings emanated from our study of the phenotype of an ultra-rare disease, Saul-Wilson syndrome. First, although not all patients were born with weight or length more than 2SD scores below the mean, all developed short stature within the first year of life, and none exhibited any catch-up growth. To put this into

perspective, stature was generally lower than the mean for achondroplasia throughout their lifetimes. Second, most patients have a progeroid appearance during early infancy. The forehead is prominent throughout their lives, but is mainly round in early childhood, and becomes tall in late childhood. Blue sclerae are seen during the first few months to years of life, but then disappear. Third, neutropenia was not appreciated in the first two months of life, but was seen in all tested individuals subsequently. Fourth, the vertebral bodies become taller and the endplates irregular with age, while ivory epiphyses develop in late childhood. Short distal phalanges of fingers and toes were present from birth, and unlike other features, did not appear to change over time.

Bone abnormalities had at least two potential clinical consequences. First, the involvement of the epiphyses was a likely cause of osteoarticular pain in all three adult patients. In the case of P2.1, degenerative osteoarthritis was objectively diagnosed since her early 20s, radiographically and by direct observation at the time of surgery, leading to joint replacement on three occasions. P7.1 exhibited advanced degenerative changes of the left hip and decreased range of motion of the shoulder joints. Second, there is a suggestion of bone fragility, as four patients developed fractures, in at least one case with no known underlying trauma, and in another case with poor healing. An additional patient exhibited postsurgical nonunion, a finding also reported in the original proband in 1982,<sup>1</sup> who was not part of our cohort. Other disorders of vesicular trafficking are known to lead to bone fragility; these include SEC24D deficiency resulting in a syndromic form of osteogenesis imperfecta (OMIM 616294),<sup>16</sup> and GORAB deficiency associated with geroderma osteodysplasticum (OMIM 231070).<sup>17</sup> Recently, a patient

with juvenile osteoporosis and recurrent fractures was found to carry a *de novo*, heterozygous variant in *COPB2*,<sup>18</sup> encoding a beta subunit of the Golgi coatamer complex that has been shown to interact with different subunits of the COG complex.<sup>19</sup>

Several ocular manifestations are common in individuals with Saul-Wilson syndrome and require attention and specialized care for both the pediatric and adult patient. Lamellar cataracts appear to be common and are often noted early in childhood. Further investigation of the mechanism underlying the increased risk for cataractogenesis is required. Retinal degeneration consistent with a rod-cone dystrophy (retinitis pigmentosa) was present in all four patients who underwent detailed ophthalmic exams at the NIH Clinical Center; it was also reported in several patients whose records were reviewed. The exact mechanism for the occurrence of retinal degeneration in Saul-Wilson syndrome is not clear; however, other disorders of vesicular trafficking have been previously associated with retinal dystrophy, including Cohen syndrome<sup>20,21</sup> and deficiency of NBAS, a component of the SNARE complex.<sup>22</sup>

A novel finding in our investigation was elevation of transaminases, although liver failure did not develop in any patient. Other intracellular trafficking disorders have been associated with liver disease, including SCYL1 deficiency,<sup>23</sup> and deficiency of NBAS<sup>24</sup> and RINT1<sup>25</sup>, both subunits of the NRZ complex that participates in retrograde trafficking.<sup>26</sup> NBAS deficiency is also associated with bone fragility, presumably due to reduced collagen secretion,<sup>27</sup> while the recurrent liver disease is related to thermal susceptibility of the syntaxin 18 complex.<sup>28</sup> The latter finding is of particular interest,

since different components of the COG complex interact with syntaxins,<sup>19</sup> while RINT1 interacts directly with the COG complex.<sup>26</sup>

Intermittent neutropenia was noted in all tested individuals. This might explain the patients' frequent respiratory infections in the first years of life, although the neutropenia persisted into adulthood while the number of respiratory infections decreased over time. Neutropenia is a complication of other disorders of intracellular trafficking, such as Cohen syndrome due to *VPS13B* disease-causing variants,<sup>29</sup> severe congenital neutropenia type 5 caused by *VPS45* variants,<sup>30</sup> and adaptor protein complex 3 deficiency, causing Hermansky-Pudlak syndrome types 2 and 10<sup>31</sup>; in the latter disorders, the neutropenia is thought to be due to impaired intracellular trafficking of neutrophil elastase.<sup>32</sup> It is thus plausible that the neutropenia of Saul-Wilson syndrome could also be related to intracellular mislocalization of proteins.

Based on the identified complications of Saul-Wilson syndrome, we can begin to establish recommendations for clinical management. (1) Skeletal – odontoid hypoplasia and osteotomy considerations: Given the universal finding of odontoid hypoplasia, with frequent C1-C2 subluxation and/or spinal cord compression, best practices in peri-operative management of patients with skeletal dysplasias should be followed.<sup>33</sup> Skeletal surgery involving osteotomy should only be considered as a last resort, given poor healing and nonunion seen in a few patients. (2) Hearing – early evaluation and possible hearing aids: Since hearing loss represents a common complication, an audiologic evaluation should be performed at least yearly, or as frequently as

recommended based on prior findings. Standard treatments for hearing loss (e.g., hearing aids) should be offered. (3) Ophthalmologic – cataracts and retinal degeneration: The presence of lamellar cataract needs to be assessed by a pediatric ophthalmologist and followed up for progression. If the cataract is dense enough to require surgery, this needs to be addressed to avoid the risk of amblyopia. Similarly, an ophthalmologic evaluation for retinal degeneration is recommended on an annual basis. Standard treatments for cataracts, and night blindness (e.g., night vision scopes, selected wavelength filters) should be offered. (4) Hematologic – neutropenia and possible G-CSF: In the setting of frequent infections, G-CSF prophylaxis should be considered, while acute infections in the setting of neutropenia can be managed by therapeutic G-CSF administration as needed. (5) Neurologic – hydrocephalus: Two patients underwent shunt placement for hydrocephalus. However, another patient with communicating hydrocephalus diagnosed in infancy had spontaneous resolution upon reimaging at 2 years of age. Thus, the possibility exists that individuals with Saul-Wilson syndrome might be predisposed to developing “benign external hydrocephalus”, an entity associated with macrocephaly and increased volume of the subarachnoid space due to decreased absorption of the cerebrospinal fluid, with spontaneous resolution within the first few years of life.<sup>34</sup> It is unclear whether a conservative approach is indicated in most cases, but insertion of a shunt seems advisable for children showing signs of increased intracranial pressure. (6) Nutrition – gastrostomy: Three patients underwent gastrostomy tube insertion. This likely represents an attempt by well-intended physicians to improve the child’s growth; however, overfeeding should be avoided. (7) Genetic counseling: Although most individuals show *de novo* inheritance of

the pathogenic variant, sib recurrence was observed in one family (1/13), probably due to germline mosaicism in a parent; thus, the recurrence risk in siblings of a proband is greater than that of the general population.

In summary, we have carefully delineated the phenotype of Saul-Wilson syndrome, providing improved understanding of the morbidity of the disease and allowing for better surveillance and management of affected individuals.

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## SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at

<http://www.nature.com/gim>

## REFERENCES

1. Saul RA. Unknown cases. *Proceedings of the Greenwood Genetic Center*. 1982;1(1):102-105.
2. Saul RA, Wilson WG. A “new” skeletal dysplasia in two unrelated boys. *Am J Med Genet*. 1990;35(3):388-393.
3. Saul RA, Wilson WG. COMMENTARY-The Saul-Wilson syndrome from its early days until now. *Am J Med Genet A*. December 2018. doi:10.1002/ajmg.a.8
4. Hersh JH, Joyce MR, Spranger J, et al. Microcephalic osteodysplastic dysplasia. *Am J Med Genet*. 1994;51(3):194-199.
5. Ferreira CR, Xia Z-J, Clément A, et al. A Recurrent De Novo Heterozygous COG4 Substitution Leads to Saul-Wilson Syndrome, Disrupted Vesicular Trafficking, and Altered Proteoglycan Glycosylation. *Am J Hum Genet*. 2018;103(4):553-567. doi:10.1016/j.ajhg.2018.09.003
6. Gahl WA, Wise AL, Ashley EA. The Undiagnosed Diseases Network of the National Institutes of Health: A National Extension. *JAMA*. 2015;314(17):1797-1798.
7. Gahl WA, Mulvihill JJ, Toro C, et al. The NIH Undiagnosed Diseases Program and Network: Applications to modern medicine. *Mol Genet Metab*. 2016;117(4):393-400.



8. Ramoni RB, Mulvihill JJ, Adams DR, et al. The Undiagnosed Diseases Network: Accelerating Discovery about Health and Disease. *Am J Hum Genet.* 2017;100(2):185-192.
9. WHO Multicentre Growth Reference Study Group. *WHO Child Growth Standards: Length/Height-for-Age, Weight-for-Age, Weight-for-Length, Weight-for-Height and Body Mass Index-for-Age: Methods and Development.* Geneva: World Health Organization; 2006.  
[https://www.who.int/childgrowth/standards/velocity/technical\\_report/en/](https://www.who.int/childgrowth/standards/velocity/technical_report/en/). Accessed November 13, 2019.
10. WHO Multicentre Growth Reference Study Group. *WHO Child Growth Standards: Growth Velocity Based on Weight, Length and Head Circumference: Methods and Development.* Geneva: World Health Organization; 2009.  
[https://www.who.int/childgrowth/standards/technical\\_report/en/](https://www.who.int/childgrowth/standards/technical_report/en/). Accessed November 13, 2019.
11. Cole TJ, Green PJ. Smoothing reference centile curves: the LMS method and penalized likelihood. *Stat Med.* 1992;11(10):1305-1319.
12. Freeman JV, Cole TJ, Chinn S, Jones PR, White EM, Preece MA. Cross sectional stature and weight reference curves for the UK, 1990. *Arch Dis Child.* 1995;73(1):17-24. doi:10.1136/ad.73.1.17
13. Cole TJ, Freeman JV, Preece MA. British 1990 growth reference centiles for weight, height, body mass index and head circumference fitted by maximum penalized likelihood. *Stat Med.* 1998;17(4):407-429.

14. Merker A, Neumeyer L, Hertel NT, et al. Growth in achondroplasia: Development of height, weight, head circumference, and body mass index in a European cohort [FRI-0298]. *Am J Med Genet A*. 2018;176(8):1723-1734. doi:10.1002/ajmg.a.38853
15. McDowell MA, Brody DJ, Hughes JP. Has age at menarche changed? Results from the National Health and Nutrition Examination Survey (NHANES) 1999-2004. *J Adolesc Health*. 2007;40(3):227-231. doi:10.1016/j.jadohealth.2006.10.002
16. Garbes L, Kim K, Rieß A, et al. Mutations in SEC24D, encoding a component of the COPII machinery, cause a syndromic form of osteogenesis imperfecta. *Am J Hum Genet*. 2015;96(3):432-439.
17. Hennies HC, Kornak U, Zhang H, et al. Geroderma osteodysplastica is caused by mutations in SCYL1BP1, a Rab-6 interacting golgin. *Nat Genet*. 2008;40(12):1410-1412.
18. Marom R, Burrage LC, Jain M, et al. COPB2 Loss of Function Leads to Disrupted Collagen Trafficking and Juvenile Osteoporosis. *Journal of Bone and Mineral Research: The Official Journal of the American Society for Bone and Mineral Research*. 2018;33(S1):76.
19. Willett R, Ungar D, Lupashin V. The Golgi puppet master: COG complex at center stage of membrane trafficking interactions. *Histochem Cell Biol*. 2013;140(3):271-283.
20. Kivitie-Kallio S, Summanen P, Raitta C, Norio R. Ophthalmologic findings in Cohen syndrome. A long-term follow-up. *Ophthalmology*. 2000;107(9):1737-1745. doi:10.1016/s0161-6420(00)00279-7

21. Chandler KE, Biswas S, Lloyd IC, Parry N, Clayton-Smith J, Black GCM. The ophthalmic findings in Cohen syndrome. *Br J Ophthalmol*. 2002;86(12):1395-1398. doi:10.1136/bjo.86.12.1395
22. Segarra NG, Ballhausen D, Crawford H, et al. NBAS mutations cause a multisystem disorder involving bone, connective tissue, liver, immune system, and retina. *Am J Med Genet A*. 2015;167A(12):2902-2912. doi:10.1002/ajmg.a.37338
23. Lenz D, McClean P, Kansu A, et al. SCYL1 variants cause a syndrome with low  $\gamma$ -glutamyl-transferase cholestasis, acute liver failure, and neurodegeneration (CALFAN). *Genet Med*. 2018;20(10):1255-1265. doi:10.1038/gim.2017.260
24. Haack TB, Stauffer C, Köpke MG, et al. Biallelic Mutations in NBAS Cause Recurrent Acute Liver Failure with Onset in Infancy. *Am J Hum Genet*. 2015;97(1):163-169. doi:10.1016/j.ajhg.2015.05.009
25. Cousin MA, Conboy E, Wang J-S, et al. RINT1 Bi-allelic Variations Cause Infantile-Onset Recurrent Acute Liver Failure and Skeletal Abnormalities. *Am J Hum Genet*. 2019;105(1):108-121. doi:10.1016/j.ajhg.2019.05.011
26. Tagaya M, Arasaki K, Inoue H, Kimura H. Moonlighting functions of the NRZ (mammalian Dsl1) complex. *Front Cell Dev Biol*. 2014;2:25. doi:10.3389/fcell.2014.00025
27. Balasubramanian M, Hurst J, Brown S, et al. Compound heterozygous variants in NBAS as a cause of atypical osteogenesis imperfecta. *Bone*. 2017;94:65-74. doi:10.1016/j.bone.2016.10.023

28. Stauffer C, Haack TB, Köpke MG, et al. Recurrent acute liver failure due to NBAS deficiency: phenotypic spectrum, disease mechanisms, and therapeutic concepts. *J Inherit Metab Dis*. 2016;39(1):3-16. doi:10.1007/s10545-015-9896-7
29. Kolehmainen J, Black GCM, Saarinen A, et al. Cohen syndrome is caused by mutations in a novel gene, COH1, encoding a transmembrane protein with a presumed role in vesicle-mediated sorting and intracellular protein transport. *Am J Hum Genet*. 2003;72(6):1359-1369.
30. Vilboux T, Lev A, Malicdan MCV, et al. A congenital neutrophil defect syndrome associated with mutations in VPS45. *N Engl J Med*. 2013;369(1):54-65. doi:10.1056/NEJMoa1301296
31. Ammann S, Schulz A, Krägeloh-Mann I, et al. Mutations in AP3D1 associated with immunodeficiency and seizures define a new type of Hermansky-Pudlak syndrome. *Blood*. 2016;127(8):997-1006. doi:10.1182/blood-2015-09-671636
32. Benson KF, Li F-Q, Person RE, et al. Mutations associated with neutropenia in dogs and humans disrupt intracellular transport of neutrophil elastase. *Nat Genet*. 2003;35(1):90-96. doi:10.1038/ng1224
33. White KK, Bompadre V, Goldberg MJ, et al. Best practices in peri-operative management of patients with skeletal dysplasias. *Am J Med Genet A*. 2017;173(10):2584-2595. doi:10.1002/ajmg.a.38357
34. Zahl SM, Egge A, Helseth E, Wester K. Benign external hydrocephalus: a review, with emphasis on management. *Neurosurg Rev*. 2011;34(4):417-432. doi:10.1007/s10143-011-0327-4

## **FIGURE TITLES AND LEGENDS:**

### **Figure 1. Phenotypic traits of patients with Saul-Wilson syndrome.**

(A-D) Progeroid features seen in the first few months of life (A, P2.1; B, P5.1; C, P6.1; D, P7.1). In addition, wrist contractures can be seen in (A), blue sclerae in (A) and (D), and boots and bar treatment for clubfoot in (C). (E-H) Facial features seen during early childhood (E, P1.1; F, P5.1; G, P6.1; H, P10.1). Note prominent, round forehead with prominent scalp veins in all. (I-L) Facial features seen in late childhood (I, P7.1; J, P5.1; K, P6.1; L, P10.1). The forehead is still prominent, but mainly tall rather than round. (M-N) Facial features in adolescence (M, P2.1; N, P7.1). (O-P) Facial features in adulthood (O, P2.1; P, P7.1). (Q-T) Feet in P1.1 at 4 years old (Q), P9.1 at 9 years old (R), P7.1 at 27 years old (S), and P2.1 at 29 years old (T). Note short distal phalanges in all, and metatarsus varus in (Q). (U-X) Hands in P1.1 at 4 years old (U), P4.1 at 5 years old (V), P9.1 at 9 years old (W), and P7.1 at 27 years old (X). Note short distal phalanges of variable degree in all.

### **Figure 2. Ophthalmologic findings.**

Clinical imaging of the ocular fundus, psychophysical testing, and electroretinography in individuals with Saul-Wilson Syndrome. (A) Color fundus photography (CFP) of left eye of P1.1 obtained under anesthesia using a portable device (RetCam3) and showing mottling of the retinal pigment epithelium (yellow arrows) and an elevated lesion inferior to the optic nerve head (white arrow). Image clarity is reduced by the presence of lamellar cataract. (B) Bioptigen optical coherence tomography indicates preserved central retina including absence of macular cystic changes and normal ellipsoid zone

(EZ) layer in P1.1. (C, F) CFP of the right and (I) left eye of affected individuals showing characteristic features of rod-cone dystrophies including attenuated retinal vessels, waxy pallor of optic nerve head, and midperipheral bony spicules (yellow arrowheads) (C, P2.1; F: P7.1; I: P10.1). (D, G) Fundus autofluorescence (FAF) images of the right eye and (J) left eye of affected individuals showing pigment deposition as hypoautofluorescence (yellow arrowheads) and a characteristic hyperautofluorescence ring (white arrowheads) typically seen in rod-cone dystrophies (D: P2.1; G: P:7.1; J: P10.1). (E, H) Cirrus optical coherence tomography scans of the right eye and (K) left eye of affected individuals ranging from an almost normal scan in (E) to loss of ellipsoid zone EZ-band (yellow arrowheads) in (H) as well as presence of macular cystic changes in (H, K) (white arrowheads) (E: P2.1; H: P7.1; K: P10.1). (L, M) Kinetic perimetry of P2.1 and P7.1, respectively, showing different degrees of constriction and midperipheral scotomata. (N) Representative electroretinography (ERG) from P2.1 showing a reduction and delay of the scotopic responses to a greater degree than the photopic ones, confirming the presence of a rod-cone dystrophy.

**Figure 3. Length/height expressed as standard deviation scores.**

Note a sharp decline in SD scores during the first few months of life, with an eventual plateau around -4 to -8.5 SD scores. Growth is near or below the mean stature for achondroplasia (dashed line).

**Figure 4. Radiographs depicting skeletal features of individuals with Saul-Wilson syndrome.**

(A-E) Radiographs of lateral cervical spine in P4.1 at 8 months (A), P5.2 at 1 year 11 months (B), P3.1 at 2 years 6 months (C), P5.1 at 6 years 1 month (D), and P7.1 at 11 years 6 months (E). Note hypoplasia of the odontoid process in all (arrows). (F-J) Radiographs of lateral lumbar spine in P4.1 at 3 months old (F), P6.1 at 5 years 10 months (G), P5.1 at 6 years 7 months (H), P10.1 at 9 years 3 months (I), and P9.1 at 12 years 5 months (J). The vertebral bodies become taller and more irregular with age. Note hypoplasia of L1 in (G, H, I). (K-O) Radiographs of lower extremities in P7.1 at 23 days (K), P10.1 at 9 weeks (L), P8.1 at 6 months (M), P5.2 at 3 years 10 months (N), and P9.1 at 12 years 5 months (O). Note proximal femoral lucencies in the first few months of life (arrows), as well as overtubulation of the long bones with slender diaphyses and metaphyseal flaring in all. (P-T) Radiographs of hands in P4.1 at 3 months (P), P13.1 at 13 months (Q), P6.1 at 6 years 9 months (R), P9.1 at 9 years 8 months (S), and P6.1 at 10 years (T). Note shortening of metacarpals and phalanges and cone-shaped epiphyses of the phalanges in all, accessory ossification centers of the proximal metacarpals (Q, R, T), and the development of squared-off ivory epiphyses (arrows) in late childhood (S, T).

**Figure 5. Relative frequency of clinical and radiographic findings in Saul-Wilson syndrome.** AF, anterior fontanelle; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

- Conflict of Interest:

The authors declare no conflict of interest.





Figure 2

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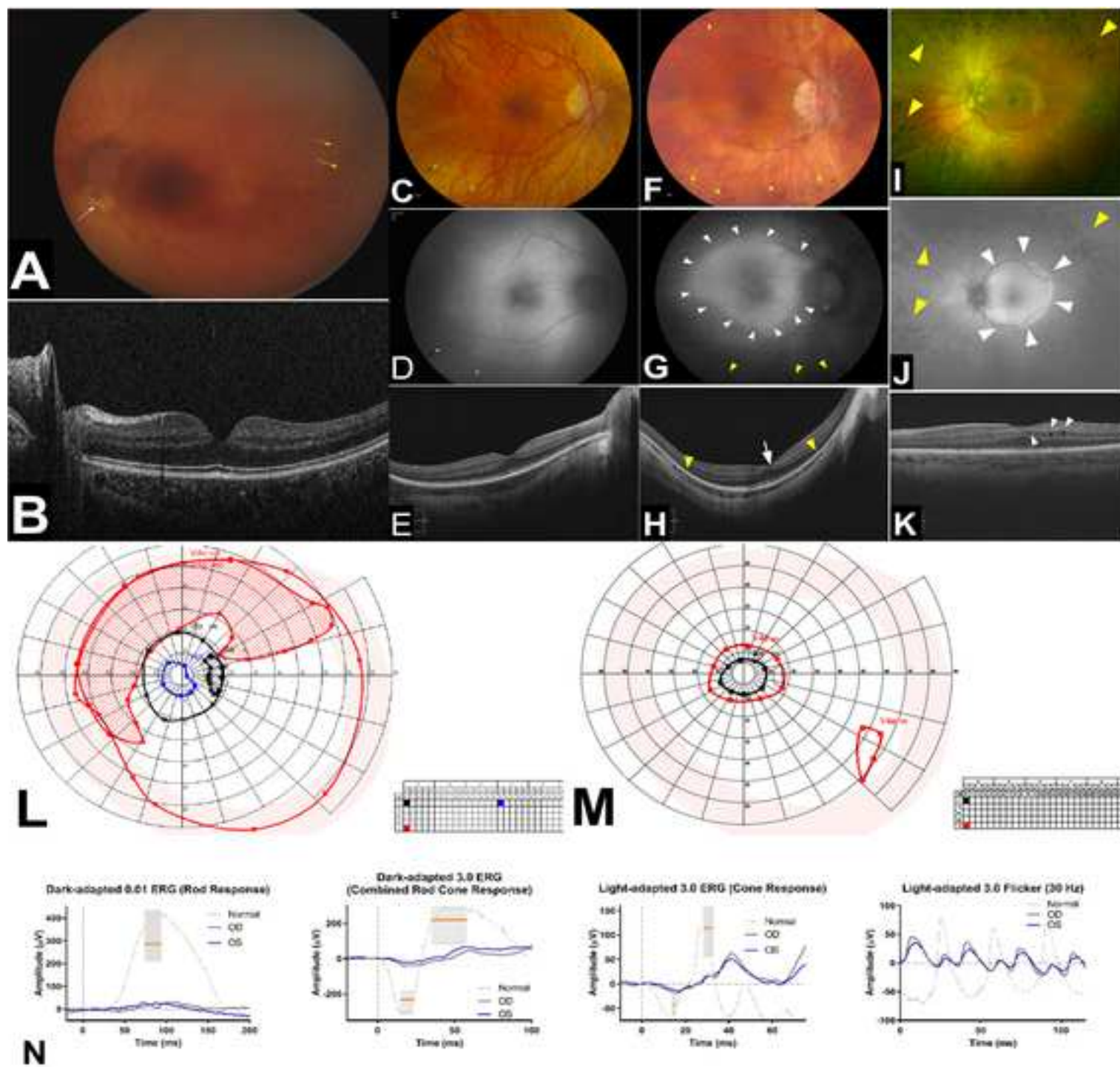


Figure 3

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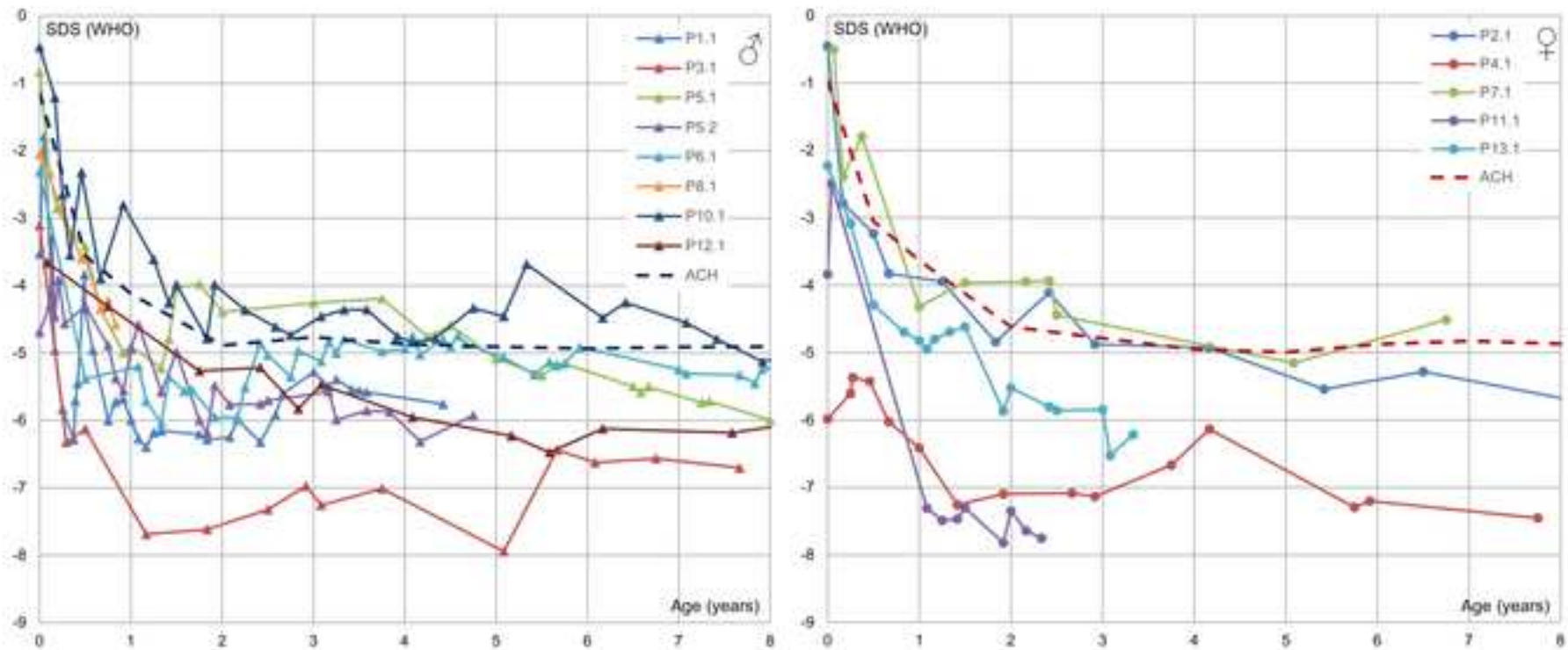




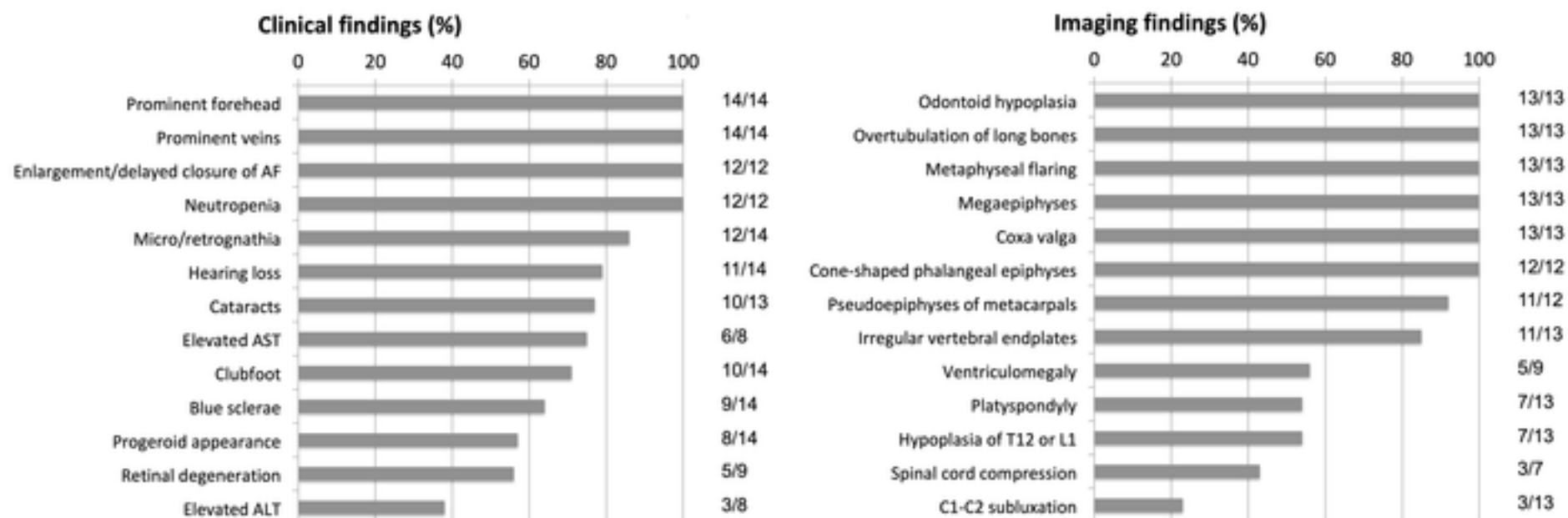
Figure 4

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Figure 5

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## **Appendix 1. Patient summaries.**

### **Patient 1.1**

This boy was born to nonconsanguineous Caucasian parents of average height. Intrauterine growth retardation was diagnosed at 20 weeks' gestation, leading to induced vaginal delivery at 36 weeks' gestation. Birth weight was 2,200 grams (CDC Z-score= -2.2; Fenton Z-score= -1.2), birth length of 43.1 cm (CDC Z-score= -2.6; Fenton Z-score= -1.7), and birth occipitofrontal circumference (OFC) of 32.7 cm (CDC Z-score= -1.4; Fenton Z-score= 0.0). At birth, talipes equinovarus was noted, along with a progeroid appearance, frontal prominence with an enlarged anterior fontanelle, prominent eyes, blue sclerae, telebrachydactyly, and micrognathia. Clubfoot was treated with serial casting. The infant failed his newborn hearing screen, and a temporal bone CT scan at 4 months of age showed a dysplastic cochlea, dilated and bulbous internal auditory canals, and mildly dilated vestibules and semicircular canals. During infancy he could only tolerate small volumes of formula, or he would otherwise regurgitate. At 6 months of age, non-obstructive ventriculomegaly was diagnosed, and at one year stenosis of the foramen magnum. During childhood, he was found to have bilateral lamellar cataracts, mild nystagmus, and an asymptomatic subaortic septal thickening without aortic valve stenosis. He had recurrent ear infections requiring myringotomy tubes three times due to ear drainage. He sat unassisted at 15 months, army crawled at 16-18 months, and walked at 24 months. He remained largely nonverbal until approximately 4 years of age, but

communicated effectively using a few hundred signs. An endocrinologic evaluation provided no indication that growth hormone secretion was deficient, and growth hormone supplementation did not lead to an increased growth velocity.

At the age of 4 years 4 months, Patient 1.1 was evaluated at the NIH Clinical Center. Despite his absolute microcephaly, his frontal prominence and more severely affected height and weight growth parameters imparted a clinical impression of relative macrocephaly. He had a high-pitched voice and an appearance of generalized lipodystrophy with prominent veins, particularly over the lateral forehead. Audiologic evaluation revealed a mild-to-moderate hearing loss that was mixed for the low-to-mid frequencies and sensorineural for the high frequencies in the left ear, with a slightly rising moderate-to-moderately severe mixed hearing loss for the entire frequency range in the right ear. Neuroimaging revealed the interval growth of a soft tissue pannus surrounding the odontoid process of the axis, resulting in severe stenosis of the central spinal canal at the level of C1, but with no abnormal signal of the spinal cord. An ophthalmologic evaluation revealed night blindness, and optical coherence tomography confirmed peripheral retinal atrophy. He also had marked optic nerve elevation, thought to be either pseudopapilledema from optic nerve shortening, or true papilledema from increased intracranial pressure. On formal neurodevelopmental evaluation, despite a previous diagnosis of global developmental delay, several of his cognitive skills were in the average range for his age. In fact, he presented

a complex and varied profile with greatest challenges in the domains of language (receptive, expressive, and verbal comprehension) and processing speed; visual spatial skills and working memory skills were areas of strength.

### **Patient 2.1**

The clinical and radiographic findings of this Caucasian patient, until the age of 4 years 8 months, were previously reported.<sup>1</sup> In summary, she was born at term with bilateral clubfoot treated with serial casting, and a diagnosis of neonatal progeria was initially entertained. For the first few months of life she exhibited feeding difficulty, hypotonia and mild gross motor delays. She developed recurrent otitis media necessitating myringotomy tubes, initially placed at 8 months old. A spinal MRI at 2 years of age showed a lumbosacral syrinx and tethered cord, the latter requiring a surgical release. Lamellar cataracts were diagnosed at 2 years old, and at that time a diagnosis of Hallermann-Streiff syndrome was entertained. She underwent left lens extraction at 3 years old. She underwent left clubfoot repair at 2 years old, and required multiple surgical revisions at 3, 9 and 12 years old. At the age of 14 years, she was diagnosed with cervical spine instability with compression of the spinal cord at C1, necessitating a cervical spine fusion. She underwent gingival graft for recession at the ages of 16 and 18 years. At 17 years of age, she was started on oral contraceptives for ovarian cysts, and at the same age was diagnosed with night blindness. At 21 years of age, she developed acute right shoulder pain and was given a diagnosis of degenerative joint disease, necessitating total shoulder



arthroplasty at 22 years of age; at the time of surgery, pertinent findings included bone-on-bone articulation between the humeral head and glenoid, and numerous subchondral cysts of the glenoid. Similarly, at 25 years of age she underwent a right hip arthroplasty, and then at 26 years, a left shoulder arthroplasty. At 22 years of age she was diagnosed with osteoporosis and received weekly alendronate, which she continued for the next six years before switching to teriparatide for one year. In retrospect, however, her low bone mineral density on dual-energy X-ray absorptiometry (DXA) seemed falsely low, as the height-corrected bone mineral density was normal even before initiation of treatment. At age 23, she graduated college. At age 24, she was diagnosed with mild-to-moderate bilateral sensorineural hearing loss, which has remained stable over time. An ophthalmologic evaluation at 29 years of age revealed bilateral cone-rod dystrophy with pigmentary retinopathy. Wechsler Adult Intelligence Scale - Fourth Edition (WAIS-IV) showed a full-scale IQ of 82 ( $m=100$ ,  $SD=15$ ). Her verbal skills were in the average range, while working memory was in the borderline range.

### **Patient 3.1**

This boy was the 3<sup>rd</sup> child to a nonconsanguineous couple of average height and German descent. He was born at 37 weeks 2 days' gestation, with a birth weight of 1,850 grams (CDC Z-score= -2.7; Fenton Z-score= -2.8), birth length of 44 cm (CDC Z-score= -2.3; Fenton Z-score= -1.9), and birth occipitofrontal head circumference of 30 cm (CDC Z-score= -2.6; Fenton Z-score= -2.4). Placental

weight was only 460 gm, without infarcts. At birth, he was noted to have a large fontanelle, low-set ears, periorbital edema, small thorax, right-sided hydrocele, and clinodactyly of the fifth fingers. Ultrasound exams of the head, hips and kidneys were unremarkable. He had a 3-week neonatal hospital stay due to feeding difficulties. A possible diagnosis of Russell-Silver syndrome was entertained at the time.

At age 3 months, he underwent a gastrostomy tube insertion to increase caloric intake, and had repeated upper airway infections associated with obstructive sleep apnea. Over time, he developed prominent scalp veins and relative macrocephaly. Hydrocephalus was suspected, but a repeat head ultrasound revealed no ventriculomegaly. Nearly no expressive language was observed during the first two years. Hearing evaluations were difficult to interpret given the inability to perform otoacoustic emissions, as well as frequent airway infections, but he was deemed to have normal hearing. He also had motor delays, as at 13 months, he was still unable to sit independently. He was also noted to have thin skin with lack of subcutaneous fat, and he exhibited severe growth delay. He continued to have feeding difficulties with poor intake, necessitating ongoing use of his gastrostomy tube.

During the first few years of life he developed frequent upper and lower respiratory infections, some of them associated with elevated CRP

concentrations and leukopenia. Neutropenia was observed, although anti-neutrophil antibodies were not found.

Ophthalmologic exam revealed bilateral hyperopia (+4 diopters) and bilateral pseudopapilledema; there were no signs of increased intracranial pressure. At 20 months of age, intermittent right-sided horizontal nystagmus was observed, but resolved spontaneously. He was diagnosed with bilateral cortical cataracts at the age of 7 years, and a surgical procedure is being planned in the near future.

At the age of 5 years he developed acute idiopathic thrombocytopenic purpura with intraoral bleeding, which was treated with platelet transfusions, intravenous immunoglobulin, and steroids. Given the prior episodes of neutropenia and now thrombocytopenia, a bone marrow biopsy was performed, and was unremarkable.

He started elementary school at the age of 7 years. By then, his motor development had improved significantly. His speech improved dramatically after school enrollment, although he uses mostly 2-3 word sentences, and his speech still remains somewhat unintelligible. His cognitive function, and especially memory, seems primarily unaffected.

#### **Patient 4.1**

This girl is the only child of a nonconsanguineous couple of Brazilian descent. The father had congenital bilateral clubfoot. The girl was conceived via in vitro fertilization due to reduced paternal sperm motility. The pregnancy was complicated by maternal hypertension from 21 weeks' gestation. Prenatal ultrasound revealed intrauterine growth restriction at 24 weeks' gestation, with shortened femora and humeri. The patient was born at 36 weeks' gestation via Caesarean section, with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. Birth weight was 1,450 grams (CDC Z-score= -3.8; Fenton Z-score= -3.0), birth length was 38 cm (CDC Z-score= -5.1; Fenton Z-score= -3.3), and birth occipitofrontal head circumference was 29 cm (CDC Z-score = -3.9; Fenton Z-score= -2.2). The patient remained in the neonatal intensive care unit for 38 days due to poor weight gain. Right talipes equinovarus was noted at birth, and treated with serial casting, followed by an Achilles tenotomy at 3 months of age. At 3 months of age she exhibited severe growth failure, relative macrocephaly with triangular facies, brachycephaly, broad forehead, biparietal prominence, enlarged anterior fontanelle, proptosis, and rhizomelic shortening of the upper extremities. A head CT scan at 3 months of age disclosed a benign subdural effusion. An ophthalmologic evaluation at 5 months of age revealed bilateral hyperopia (OD +3.00, OS +3.75). At 1 year of age, she had diffuse reduction of subcutaneous adipose tissue, prominent veins in the scalp and abdomen, and sparse hair and eyebrows. She started walking at 20 months of age, and her anterior fontanelle closed by 21 months of age. She had four episodes of otitis media between 2 and 4 years of age. At 4 years old, she had increased thoracic

kyphosis, restriction of elbow extension, enamel defects, some degree of speech delay, and a hypernasal voice. At 7 years of age, her height was 82 cm ( $Z = -4.9$ ), weight 9.49 kg ( $Z = -7.7$ ), occipitofrontal circumference 48.5 cm ( $Z = -2.4$ ), arm span 73 cm, and sitting height 45.5 cm. By the last examination, she had bilateral moderate mixed hearing loss, not present during a prior evaluation at 1 year of age.

### **Patient 5.1**

This boy was conceived to nonconsanguineous Caucasian parents of average height. Pregnancy was complicated by intrauterine growth retardation and left hydronephrosis. Delivery was by emergent Caesarean section at 37 weeks' gestation due to non-reassuring fetal heart rate. Birth weight was 2,240 grams (CDC Z-score = -2.1; Fenton Z-score = -1.6), birth length was 48.3 cm (CDC Z-score = -0.7; Fenton Z-score = 0.0), and birth occipitofrontal head circumference was 33 cm (CDC Z-score = -1.3; Fenton Z-score = -0.2). He failed his newborn hearing screen and received phototherapy for jaundice in the newborn nursery. He underwent casting at 3 days of age for right clubfoot, and was discharged to home at 5 days of age. He had a ventriculoperitoneal shunt placed at 6 months of age for hydrocephalus, and a gastrostomy tube placed at 8 months of age.

He had many hospitalizations in his first 2 years of life for pneumonia, RSV, and other respiratory infections. An endocrinologic evaluation at 5 years of age noted only low IGF1 levels; he passed two growth hormone stimulation tests at 6 and 7

years of age. He was admitted at 7 years of age for left ureteropelvic junction obstruction secondary to constipation, treated with bowel cleanout. Myringotomy tubes were placed multiple times, last at 7 years of age, due to chronic effusions bilaterally leading to conductive hearing loss. He had an adenotonsillectomy at 7 years of age due to recurrent streptococcal pharyngitis. An immunologic evaluation noted normal IgG, IgA, IgE, and IgM levels and normal diphtheria and tetanus titers. Intermittent neutropenia prompted a bone marrow aspiration, which yielded unremarkable results. Dental evaluation revealed advanced eruption of secondary teeth; a molar had erupted by 8 years of age. Also at 8 years old, he underwent surgical treatment for ureteropelvic junction obstruction.

Developmentally, he started walking at 2 years of age. At age 8 years he is doing well in school and reading above grade level.

At his last clinical evaluation at age 8 years, he had mild-to-moderately severe conductive hearing loss, slightly worse on the right side, with hearing grossly normal for conversation. He had developed bilateral cataracts and exhibited bilateral exophoria, myopia, anisometropia, and an anatomical narrow angle. He did not have any acute or chronic joint pain. He was grossly normocephalic with bifrontal bossing, and a triangular facies; the external scalp vessels were visible. The sclerae were white and not injected; palpebral fissures were horizontal. External ears had normal structure and position. The teeth appeared to be of mixed dentition, with dental crowding. From the musculoskeletal standpoint,

there was proportionate short stature with anterolateral rib flaring. Clinically, there was no evidence of scoliosis, kyphosis or lordosis. Elbows lacked approximately 40 degrees from full extension, but otherwise range of motion at the elbows, wrists and knees was full. Telebrachydactyly was noted, and the left fourth and fifth fingers showed camptodactyly. Pes planus was noted. His neurologic examination was normal.

## **Patient 5.2**

This male is a full sibling to patient 5.1. Pregnancy was complicated by gestational diabetes treated at first by diet and then with oral medication in the third trimester. Prenatal monitoring noted supraventricular tachycardia, for which his mother was treated during the late second to early third trimester, and admitted for 3 weeks of the pregnancy. Polyhydramnios was noted in the second trimester. Delivery was by emergent Caesarean section at 32 weeks 4 days' gestation due to non-reassuring fetal heart tones and failure to progress. Birth weight was 1,750 grams (CDC Z-score= -2.9; Fenton Z-score= -0.4), birth length was 41 cm (CDC Z-score= -3.4; Fenton Z-score= -0.7), and birth occipitofrontal head circumference was 31.5 cm (CDC Z-score= -1.9; Fenton Z-score= 1.1). Supraventricular tachycardia was not present after birth. The infant had normal head ultrasound exams in the nursery, where he had an extended stay due to prematurity. He failed his newborn hearing screen due to conductive loss. He was discharged to home at 5 weeks of age.

Multiple myringotomy tubes were placed for chronic mucoid and serous effusion, with concurrent adenoidectomy. There were no further surgeries, but he did have a femur fracture after falling off a swing at 2 years old, which was treated with reduction and a spica cast. His anterior fontanelle was still open at 2.5 years of age, measuring 4x4 cm.

At his last clinical evaluation at 3 years 10 months of age, he wore glasses due to hyperopia and accommodative esotropia (OD +3.50, OS +3.00+00.50x139); no cataracts were detected. He was grossly normocephalic with bifrontal bossing and triangular facies. The fontanelles were closed. The external scalp vessels were visible, but not prominent. The sclerae were white and not injected; palpebral fissures were horizontal. External ears had normal structure and position. Dental crowding was present. From the musculoskeletal standpoint, there was proportionate short stature. Clinically, there was no evidence of scoliosis, thoracolumbar kyphosis, or lordosis. Elbows lacked approximately 40 degrees from full extension, but otherwise range of motion at the elbows, wrists and knees were full. Telebrachyphalangy was noted. Pes planus was noted. Neurologic examination was normal.

### **Patient 6.1**

This boy was born at 37 weeks' gestation to nonconsanguineous Caucasian parents. Pregnancy was complicated by intrauterine growth restriction with short femurs noted in the third trimester. Birth weight was 2,180 grams (CDC Z-score=



-2.2; Fenton Z-score= -1.8), birth length was 45.5 cm (CDC Z-score= -1.7; Fenton Z-score= -1.2) and birth occipitofrontal circumference was 30.5 cm (CDC Z-score= -2.4; Fenton Z-score= -1.9). He exhibited talipes equinovarus and a disproportionately large head with prominent scalp veins. He spent time in the neonatal intensive care unit due to respiratory distress and failure to gain weight. He received serial casting for talipes equinovarus and subsequently underwent heel cord tenotomy. He also had a tethered cord, and ultrasound performed shortly after birth showed bilateral mild-to-moderate hydronephrosis, which resolved spontaneously. He passed his newborn hearing screen but failed a sedated auditory brain response exam (bilaterally) at 6 months of age.

A brain MRI obtained at 5 months of age showed communicating hydrocephalus. Follow-up MRI at 2 years of age showed resolution of the hydrocephalus without other anomalies. During infancy he had frequent neutropenia with negative anti-neutrophil antibody testing, associated with bouts of pneumonia that resolved by the age of 2 years. His anterior fontanelle was still open at 3 years of age. Recurrent otitis media prompted placement of myringotomy tubes at 3 years of age. A prior history of speech delay required speech therapy, but he is currently doing well in school with no cognitive problems, and he does not require any specialized therapies. He was followed by cardiology for a patent foramen ovale and had aortic dilation on echocardiogram. At 9 years 11 months of age, his aortic annulus measured 1.72 cm (Z-score 2.57), aortic root 2.33 cm (Z-score

2.5), sinotubular junction 1.90 cm (Z-score 1.85) and ascending aorta 2.30 cm (Z-score 3.24).

Ophthalmologic evaluation identified hyperopia and cataracts, requiring bilateral phakectomy. The patient has received growth hormone supplementation since 3 years of age at a dose 0.23-0.36 mg/kg/week, with modest improvement in height.

A diagnosis of microcephalic osteodysplastic primordial dwarfism type 2 was postulated based on review of radiographs. Other diagnoses entertained over the course of his life included progeria, Wiedemann-Rautestrauch syndrome, mandibuloacral dysplasia, Seckel syndrome, Russell-Silver syndrome, Hallermann-Streiff syndrome, and Meier-Gorlin syndrome.

Developmental assessment at 9 years of age using the Reynolds Intellectual Assessment Scales showed a verbal intelligence index of 104, nonverbal intelligence index of 118, composite memory index of 115, and composite intelligence index of 111.

At age 10 years, the boy had a 9-degree dextrocurvature of the upper thoracic spine (T2-T6) and 4-degree levocurvature of the midthoracic spine (T6-T9), with 11-degree levoscoliosis of the thoracolumbar spine (T9-L2) and 9-degree levocurvature of the lumbar spine (L2-L5).

At the age of 11 years, he exhibits bilateral conductive hearing loss, for which he wears hearing aids.

### **Patient 7.1**

This Caucasian girl was delivered at 39 weeks' gestation via Caesarean section, after a pregnancy complicated by oligohydramnios from 2.5 weeks of amniotic fluid leak prior to delivery. Her birth weight was 1,960 grams (CDC Z-score= -2.8; Fenton Z-score= -3.2). At the time of delivery, she had contractures of her elbows, knees and calcaneovalgus deformities of her feet, which resolved spontaneously over the next few weeks, except for some mild restriction of elbow and knee extension that persisted over the years. She had several apneic episodes that had resolved by two weeks of life. A physical exam at 3 weeks of life revealed a distinctive appearance with translucent skin over her face and head with prominence of the veins, midface hypoplasia with shallow orbits and exophthalmos, a prominent nasal bridge with slight beaking of the tip of the nose, and an enlarged anterior fontanelle. As a toddler, she had recurrent otitis media, and was diagnosed with high myopia. Diagnoses that were initially entertained included pycnodysostosis, osteogenesis imperfecta, and Hallermann-Streiff syndrome. At 5 years of age, she was clinically diagnosed with Saul-Wilson syndrome, at which time her height was 85 cm, weight 10.7 kg, and head circumference 49 cm. She had wedging of T12 and odontoid hypoplasia with some instability (4 mm of translation), mild pectus carinatum, mild thoracic

kyphosis, and short distal phalanges. She had pigmentary changes of the retina that spared the macula but produced a blotchy appearance of the retinal periphery. At 6 years of age her refractive error was -3.00 -.25 x 30 OD and -4.00 -2.25 x 30 OS. At 13 years old she received hearing aids for moderate-to-severe conductive hearing loss in the right ear, and moderate-to-profound conductive hearing loss in the left ear. She was found to have tympanosclerosis with ossicular fixation.

Surgical history included myringotomy tube placement and adenoidectomy by 5 years of age, and left tympanoplasty at 13 years of age. Also at 13 years of age she underwent bilateral shelf acetabuloplasty and bilateral femoral varus osteotomy to treat severe bilateral acetabular dysplasia that had caused disabling hip pain. At age 16, she had a hip revision due to nonunion on the right side leading to pain; this included repeat osteotomy of the right proximal femur with debridement of pseudoarthrosis. Five months later she had further revision of the right proximal femoral nonunion. She had bilateral cataract removal at 21 years of age.

At 23 years of age, she had leg length discrepancy; her height was 107.1 cm and her head circumference was 51.4 cm. She avoided hard foods because her widely spaced teeth felt loosely anchored. She wore hearing aids and lacked peripheral vision. Physical exam at 27 years of age also revealed limited shoulder range of motion, to only about 75 degrees of abduction bilaterally, while

hip radiographs revealed advanced degenerative changes of the left hip. A DXA scan showed a Z-score of the anteroposterior spine (L2-L4) of -5.2 and a right 1/3 forearm Z-score of -1.1, but Z-score correction for height (assuming 20 years of age, the upper age limit allowed for this correction) corresponded to -2.48 in the lumbar spine, and +0.85 in the 1/3 radius.<sup>2</sup> Wechsler Adult Intelligence Scale - Fourth Edition (WAIS-IV) showed a full-scale IQ of 89. Scores in the Wide Range Achievement Test - 4 (WRAT4) were 79 for word reading, 81 for sentence comprehension, 81 for spelling, and 78 for reading composite (m=100, SD=15 for all scores).

### **Patient 8.1**

This boy is the first child of healthy Swedish parents of average height. Pregnancy was complicated by intrauterine growth retardation and talipes equinovarus diagnosed at 19 weeks' gestation. He was born vaginally at 41 weeks' gestation, with birth weight of 2,800 grams (CDC Z-score= -1.2; Fenton Z-score= -2.2), birth length of 46 cm (CDC Z= -1.6; Fenton Z-score= -2.8), and birth occipitofrontal head circumference of 33.5 cm (CDC Z-score= -1.1; Fenton Z-score= -1.5). The boy had mild neonatal jaundice and persistent feeding difficulties. His talipes equinovarus was treated with tenotomy of the Achilles tendon and a Mitchell-Ponseti abduction brace, which he still wears at night. He has no ocular manifestations. Neonatal hearing test was normal. He had a heart murmur, but echocardiogram was normal. His motor development was slightly delayed and he sat at eight months of age.

On his last exam at 9 months of age, the boy had relative macrocephaly, frontal bossing with an indentation in the middle of the forehead, a prominent vascular network over the skull and a large anterior fontanelle (15x15 cm). He exhibited widely spaced eyes, long eyelashes and slight proptosis. Midface hypoplasia was present, with relatively large ears, retrognathia, and small mouth with thin lips and downturned corners of the mouth. Heart sounds were normal. He has a protuberant abdomen—but no organomegaly or umbilical hernia—and a shawl scrotum. His first metacarpal was a bit short and his fingers had a slight ulnar deviation with normal nails. Range of motion of the extremities was normal throughout, with slight overextension of the knees. His back was straight, with a small sacral dimple, but no hypertrichosis.

### **Patient 9.1**

This girl was born to Canadian parents of average stature. Pregnancy was complicated by maternal insulin-dependent diabetes mellitus and prenatal ultrasound revealing bilateral shortened femurs at 31 weeks' gestation. She was born at 36 weeks' gestation, with birth weight of 2,130 grams (CDC Z-score= -2.5; Fenton Z-score= 2.0), birth length of 39 cm (CDC Z-score= -4.7; Fenton Z-score= -0.3), and birth occipitofrontal head circumference of 30.5 cm (CDC Z-score= -2.9; Fenton Z-score= 1.8). At birth, physical exam showed a widely patent anterior fontanelle measuring 8x7 cm, bilateral proptosis, downslanted palpebral fissures, micrognathia, and low-set ears.

Early developmental milestones were achieved on time; there were no developmental or hearing concerns. She was diagnosed with strabismus and myopia and was prescribed glasses at one year of age. She has peripheral vision loss. There are no known cardiac concerns. She was diagnosed with growth hormone deficiency on stimulation testing; growth hormone therapy was eventually stopped due to limited linear growth response.

At her last exam at 9 years of age, she exhibited downslanted palpebral fissures, bulbous nose, short neck, and a prominent metopic ridge. Her ears were normally formed, but low-set. She had proportional short stature with acromelia. Her hands were short and broad, with extremely short and broad fingers and redundant skin. She exhibited genu valgum, pes planus, overpronation of the ankles and feet and short, broad toes. She also displayed significant lumbar lordosis. Cardiorespiratory, abdominal, and neurologic exams were unremarkable.

A brain MRI incidentally identified a well-defined arachnoid cyst filling the sella and compressing the pituitary gland. Her echocardiogram was normal. A skeletal survey showed diffuse broadening and shortening of all phalanges, metatarsals and metacarpals. Her tibiae and fibulae had prominent proximal and distal metaphyses and epiphyses. There were also prominent distal metaphyses and epiphyses of her femurs. The iliac bones were mildly diminutive, but with normal

morphology. The hips exhibited mild broadening of the proximal femoral epiphyses and metaphyses. The vertebral bodies showed anteroinferior beaking in the thoracolumbar region, with no gibbus deformity. There was mild dextroscoliosis of the thoracolumbar spine. She had a J-shaped sella and innumerable Wormian bones. Her overall bone density was satisfactory, and her bone age was at the lower range of normal.

### **Patient 10.1**

This boy is the first child of healthy nonconsanguineous Danish parents of average height. He was born at 40 weeks' gestation via Caesarean section due to breech presentation. Apgar scores were normal. Birth weight was 2,780 grams (CDC Z-score= -1.3; Fenton Z-score= -1.8), birth length was 49 cm (CDC Z-score= -0.4; Fenton Z-score= -1.0), and birth occipitofrontal head circumference was 34 cm (CDC Z-score= -0.8; Fenton Z-score= -0.7). He had a large anterior fontanelle extending to the nasal bridge, a prominent forehead, low-set ears, contractures at the elbows and knees, and clubfoot. He developed severe failure to thrive during the first few weeks of life. At 4 months of age, a ventriculoperitoneal shunt was placed. He underwent bilateral cataract surgery at 9 months, and gastrostomy tube placement at 15 months of age. He sat independently at 9 months of age, and walked independently by 2 years of age. He was noted to have neutropenia associated with recurrent infections and requiring filgrastim administration, and additionally had hepatosplenomegaly. A bone marrow biopsy at 2 years of age showed a hyperplastic marrow; a liver



biopsy showed eosinophilic inclusions. He had a renal stone at 2 years 4 months old. He also had vitreoretinal degeneration, and wears a bone-anchored hearing aid for right-sided hearing loss. Imaging studies revealed a normal echocardiogram, normal DXA scan, head CT scan with open sutures, delayed cranial vault ossification, and subluxation of the atlas, and brain MRI with delayed myelination, hypoplastic corpus callosum, small cysts in the capsula interna, and anterior displacement of the atlas with an abnormal course of the proximal cervical medulla oblongata and pons. Methylation analysis for Russell-Silver syndrome was normal.

At 5 years 7 months, he developed a mid-diaphyseal fracture of the left femur after slipping on the floor, which was considered a low-impact fall. At 10 years 8 months of age, his weight was 16 kg ( $Z = -3.9$ ), height 105 cm ( $Z = -5.4$ ), and head circumference 51 cm ( $Z = -1.5$ ).

### **Patient 11.1**

This girl was born to healthy parents of Mexican descent. Pregnancy was complicated by asymmetric intrauterine growth retardation. She was born via vaginal delivery at 37 weeks 5 days' gestation, with birth weight of 1,810 grams (CDC Z-score = -3.1; Fenton Z-score = -3.0) and birth length of 42 cm (CDC Z-score = -3.3; Fenton Z-score = -2.6). She had a single umbilical artery, left-sided grade 3 hydronephrosis, and a patent ductus arteriosus that closed spontaneously. She stayed in the neonatal intensive care unit for poor weight

gain. She had bilateral clubfoot, and received serial casting followed by Achilles tenotomies at 11 months of age; at 23 months old, she still wears a boots and bar orthosis at night.

Her motor development has been delayed. She sat independently at 18 months and pulled to stand at 22 months old. At 23 months, she cannot crawl. She speaks two words. Her fine motor and social development appear normal.

She passed her newborn hearing screen, but speech audiometry performed at 22 months of age revealed abnormal responses to speech stimuli in the moderate hearing loss range, in at least one ear, on soundfield testing. She had otitis media and frequent upper respiratory infections. Her white blood cell count at 18 months of age was 5,510 cells/uL, with 6.2% neutrophils (absolute neutrophil count of 340/uL). Additionally, she had increased TSH and received levothyroxine supplementation at 18 months of age.

Physical examination at 23 months of age revealed an enlarged anterior fontanelle (8x4 cm), prominent forehead and scalp veins, low-set ears, prominent eyes with bluish sclerae, a thin nasal bridge with a convex nasal ridge inferiorly, and a prominent columella. There was a prominent groove along the inferior border of the rib cage, but no pectus deformity; a mild thoracolumbar gibbus was present, as well as lateral elbow prominence bilaterally and distal joint laxity. Of note, there was no telebrachydactyly.

A diagnosis of Lenz-Majewski syndrome had been entertained on clinical grounds, while a diagnosis of microcephalic osteodysplastic primordial dwarfism type 2 was entertained on radiographic grounds.

### **Patient 12.1**

This male Caucasian subject, now age 39 years, was previously described as patient 2 by Saul and Wilson<sup>3</sup>, along with an unrelated older patient who had similar physical and radiographic findings

He was born at 36 weeks' gestation, with birth weight 1.5 kg (CDC Z-score= -3.3; Fenton Z-score= -2.9). At birth, he was noted to have a large anterior fontanelle (7x7 cm), bilateral clubfoot, a prominent sternum, and knee and elbow contractures. His early weight gain and linear growth were slow, and his developmental milestones were delayed. He crawled at 12 months, walked at 3 years, and had delayed language development. Early hearing tests were normal, but he was subsequently found to have conductive hearing loss. He had frequent ear infections, and a benign cholesteatoma was removed at age 7 years. He had several focal seizures with normal EEG studies.

At 9 years of age, his height was 96.5 cm, weight 16.1 kg, and head circumference 48.9 cm. He had a prominent forehead, a narrow nasal root with a "beaked" nose, and prominent globes. His chin was small, and the teeth were

crowded and slightly opalescent. Testes were palpable high in the scrotum. The hands and fingers were short, and the fingers were broad distally, with short nails. Radiographs showed short, broad phalanges with coning and sclerosis of several phalangeal epiphyses. Although earlier bone age determinations were delayed, bone age determination at age 8 years was normal. There was delayed closure of his anterior fontanelle. An ophthalmologic exam at age 8 years was normal, but he subsequently developed mild cataracts.

He has had several episodes of pneumonia requiring hospitalization and has had intermittent neutropenia. He had a traumatic fracture of his femur at age 12 years and another femoral fracture at age 25 years that was complicated by poor healing, and he eventually needed a wheelchair. Currently, he receives opioids regularly for osteoarticular pain.

### **Patient 13.1**

This girl was the second child of a nonconsanguineous couple of average height and Korean descent. Pregnancy was complicated by intrauterine growth retardation, fetal micromelia, poorly mineralized cranium and distal spine, flat nasal bridge, and bilateral clubfoot. She was born at 39 weeks' gestation via vaginal delivery, with Apgar scores of 7 and 9 at 1 and 5 minutes, respectively. Birth weight was 2,150 grams (CDC Z-score= -2.4; Fenton Z-score= -2.6), birth length 45 cm (CDC Z-score= -2.0; Fenton Z-score= -1.9), and birth occipitofrontal head circumference 32 cm (CDC Z-score= -1.9; Fenton Z-score= -1.5). Physical

exam revealed large anterior fontanelle, short palpebral fissures, mild ptosis, malar hypoplasia, small mouth, low-set cup-shaped ears, and short limbs. She remained in the neonatal intensive care unit for 8 days due to mild respiratory distress and feeding problems. Head and renal ultrasound exams and echocardiogram were unremarkable, and she passed the newborn hearing screen. Brain MRI revealed normal sized ventricles and a cavum septum pellucidum. Bilateral talipes equinovarus was treated by serial casting followed by heel cord lengthening. She suffered a right humeral fracture at 2 months of age, in the absence of any known trauma. With respect to development, she sat up at 10 months, walked at 18 months, and spoke several words by 2 years of age. Neutropenia was evident since the first few months of life. Mild conductive hearing loss was diagnosed at 22 months of age. At 3 years of age, her growth parameters were: weight 7.7 kg ( $Z = -4.6$ ), height 71 cm ( $Z = -6.2$ ), and occipitofrontal head circumference 48.5 cm ( $Z = -0.2$ ). Arm span was 6 percent less than height, and palm and hand were at the 50<sup>th</sup> percentile for 6 and 9 months, respectively. She had a closed fontanelle, readily visible veins on her chest, full range of joint motion, and tibial bowing. Neurologic exam was unremarkable. Radiographs revealed relatively enlarged skull with Wormian bones, generalized shortening of all long bones and tubular bones in the hand, bowing of the forearms, mild epiphyseal and metaphyseal irregularity in all extremities, and mild metaphyseal cupping in the tubular bones of the hands. There were mild vertebral endplate irregularities at multiple levels as well as mild platyspondyly, and distal sacrococcygeal dysgenesis.

At 29 months, she developed periorbital cellulitis and lymphadenopathy, and given neutropenia, she received 3 days of G-CSF at 5 mcg/kg/day. Her initial ANC was 1,080/uL, improved to 1,950/uL after 3 doses, which was deemed to be a better response than that seen in many genetically determined neutropenias, but not as brisk a response as seen in patients without genetic disorders.

### **References:**

1. Hersh JH, Joyce MR, Spranger J, et al. Microcephalic osteodysplastic dysplasia. *Am J Med Genet.* 1994;51(3):194-199.
2. Zemel BS, Kalkwarf HJ, Gilsanz V, et al. Revised reference curves for bone mineral content and areal bone mineral density according to age and sex for black and non-black children: results of the bone mineral density in childhood study. *J Clin Endocrinol Metab.* 2011;96(10):3160-3169.
3. Saul RA, Wilson WG. A “new” skeletal dysplasia in two unrelated boys. *Am J Med Genet.* 1990;35(3):388-393.

## **SUPPLEMENTARY LEGENDS:**

### **Supplementary Tables:**

#### **Table S1: Ophthalmologic findings in individuals with Saul-Wilson syndrome.**

BCVA: Best corrected visual acuity; C/D: Cup-to-disc ratio; CE: Cataract extraction; CFP: Color fundus photography; CSM: Central, steady, maintained; ERG: Electroretinography; FAF: Fundus autofluorescence; LX(T): left intermittent exotropia; ND: Not determined; OCT: Optical coherence tomography; OD: right eye; ONH: Optic nerve head; OS: left eye; RCD: Rod-cone dystrophy; TAC: Teller acuity cards.

#### **Table S2: Growth parameters as measured by standard deviation scores compared to the general population.**

Scores calculated using UK90 (left) and WHO (right) reference standards. Growth parameters were corrected for gestational age. BMI, body mass index; HC, head circumference; SD, standard deviation.

### **Supplementary Figures:**

#### **Figure S1. Phenotypic findings in Saul-Wilson syndrome.**

(A) P6.1 at 2 months of age, showing a progeroid appearance, prominent forehead and visible veins, sparse eyebrows, blue sclerae, and thin vermilion of the lower lip. (B) P4.1 at 5 months of age, showing a prominent forehead with

visible veins, sparse eyebrows, blue sclerae, and thin vermilion of the upper and lower lips. (C) P8.1 at 6 months of age showing prominent forehead and veins, low-set ears, and retrognathia. (D) P10.1 at 7 months of age, showing a progeroid appearance, prominent forehead and veins, sparse eyebrows, low hanging columella, and thin vermilion of the upper and lower lips. (E) P3.1 at 14 months of age, showing prominent scalp veins. (F) P5.2 at 2 years 5 months, showing relative macrocephaly with a prominent forehead, and thin vermilion of the upper lip. (G) P5.1 at 5 years 10 months, showing prominent forehead and sparse eyebrows. (H) P2.1 at 29 years of age, showing a tall forehead, low-set ears, convex nasal ridge, and retrognathia. (I) P2.1 at 29 years, showing telebrachydactyly of toes, and metatarsus varus despite numerous surgical repairs for clubfoot.

**Figure S2. Skeletal findings.**

Top row showing radiographs from P1.1 at age 6 months (C, E, I), 2 years (A) and 4 years 4 months (B, D, F, G, H). These images show age-dependent evolution of coxa valga (A-B), slender long bones with metaphyseal flaring and large epiphyses (C-D), hypoplasia of the proximal fibula (C-D), and brachydactyly (E-F). There is also platybasia (G) and craniovertebral junction stenosis (H).

Platyspondyly is seen only at younger age (I).

Bottom row (J-N) showing radiographs from P2.1 at age 29 years of age. In the adult, note degenerative joint disease of large joints (J, L), overtubulation of the



long bones (K), Madelung-like deformity of the forearm and wrist (L-M), and tall vertebral bodies with vertebral hypoplasia at the thoracolumbar junction (N).

**Figure S3. Long bone fractures in individuals with Saul-Wilson syndrome.**

(A) P13.1 at 2 months of age showing a right humeral fracture; note in addition casting of bilateral lower extremities for treatment of clubfoot. (B) P5.2 at 2 years 9 months showing a left femoral fracture. (C) P10.1 at 5 years 7 months showing a left femoral fracture. (D) P12.1 at 30 years 2 months showing intramedullary rod as treatment for a prior left femoral fracture.

**Figure S4. Nonunion of right femur.**

(A) P7.1 at 16 years 6 months around the time of hip revision for nonunion of the right femoral osteotomy. (B) Persistence of nonunion 11 years later at 27 years 7 months. Note also degenerative joint disease of the right hip with marked joint space narrowing.

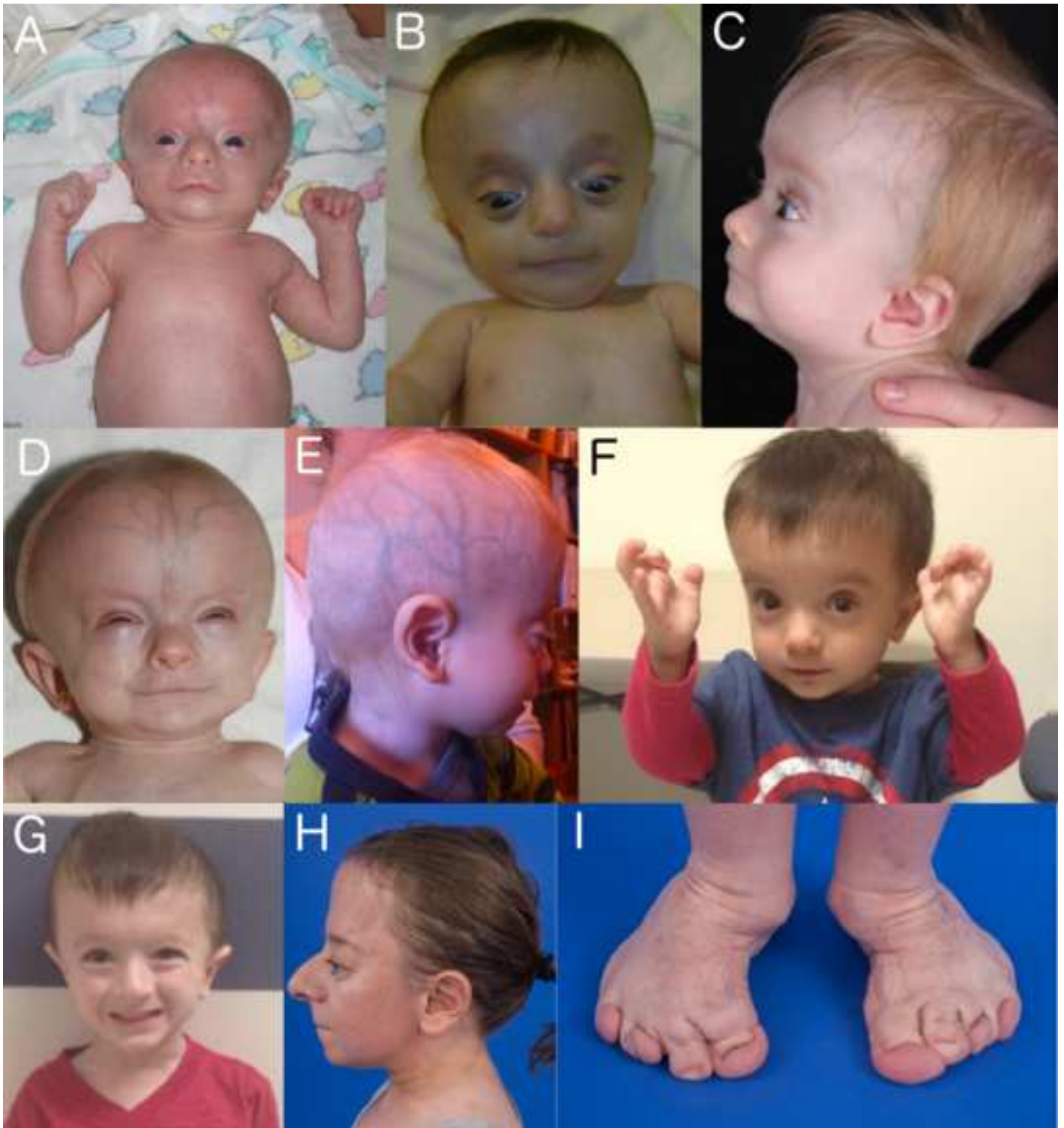
**Figure S5. Laboratory findings in Saul-Wilson syndrome.**

ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase. Red lines indicate upper limit of normal (ALT and AST) and lower limit of normal (ANC).

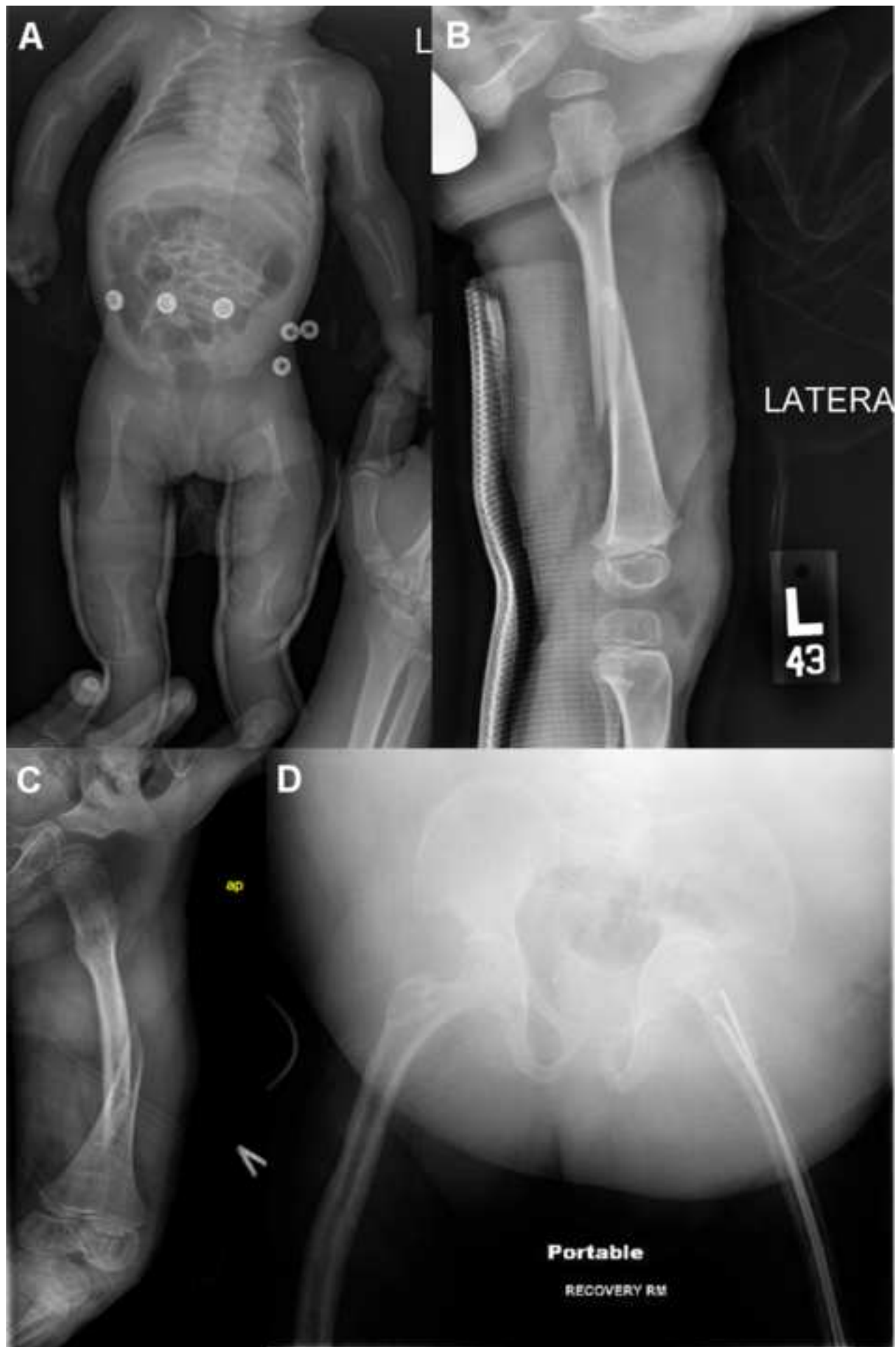
	Pt 1.1	Pt 2.1	Pt 7.1	Pt 10.1
Age (yrs)	4	29	27	11
BCVA	CSM (TAC: 20/50)	20/32 OD, 20/40 OS	20/40 OD, 20/50 OS	20/40 OD, 20/100 OS
Axial Length (mm)	20.47 / 20.13	22.51 / 23.37	23.35 / 23.35	20.30 / 20.53
Alignment	Orthophoria	Orthophoria	Orthophoria	LX(T)
Nystagmus	+	None	Few beats of nystagmus in upgaze	None
Anterior Segment	Lamellar cataract	Pseudophakia (CE at 2 and 4 yo); lamellar cataract preop	Pseudophakia (CE at 20 yo)	Pseudophakia
Retina	Preserved macula; attenuated vessels; mottling with peripheral atrophy and depigmentation	Myopic fundus with blonde pigmentation; mild vascular attenuation; peripheral bony spicules especially nasal and superior (with some inferiorly)	Posterior staphyloma; moderate to severe vascular attenuation; midperipheral spicules and retinal atrophy; chorioretinal lesions	Preserved central island, with extensive bony spicule changes and atrophy peripherally; mild vascular attenuation
Optic Nerve	C/D 0.0; elevated ONH likely drusen	C/D 0.1; trace pallor; temporal crescent	C/D 0.3; tilted; peripapillary crescent; ONH drusen	C/D 0.1
Refractive Error	+3.00 / +1.50	-6.00+3.25x180 / -7.75+6.00x170	-2.25+2.50x15 / -0.75+3.00x170	+1.75+1.50x85 OU
Color Vision	ND	D15 fail OS, scotopic axis	Pass D15 and Ishihara	Ishihara 15/16 OD and 13/16 OS
Visual Field	ND	Constricted I4e and I1e	Constricted V4e and I4e	ND
OCT	Bioptigen	Cirrus	Cirrus	Cirrus
ERG	ND	RCD	Photopic only	ND
Fundus Imaging	RetCAM	CFP, FAF	CFP, FAF	CFP, FAF

Table S2

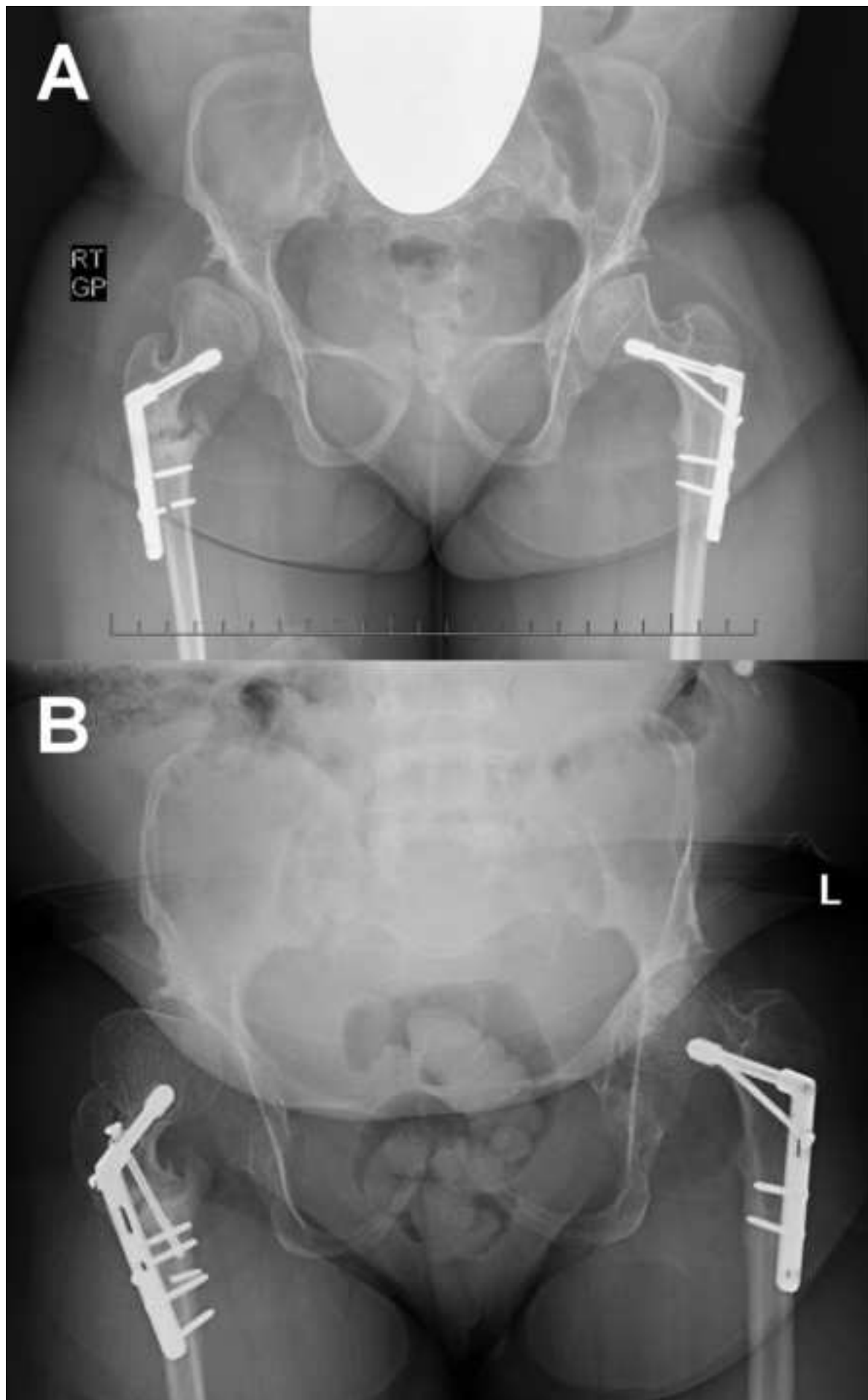
		0	0,25	0,5	0,75	1	1,5	2	3	4	5	6	7	8			0	0,25	0,5	0,75	1	1,5	2	3	4	5	6	7	8
Age Height	P1.1	-2,37	-4,93	-4,03	-4,90	-5,48	-5,66	-5,92	-5,19	-5,50					P1.1	-1,89	-5,39	-4,31	-5,25	-5,87	-6,06	-6,09	-5,28	-5,59					
	P2.1	-1,03	-3,16	-3,47	-3,76	-3,84	-4,42	-4,74	-5,05	-4,93	-5,31	-5,55	-5,80	-6,15	P2.1	-0,46	-3,09	-3,23	-3,54	-3,66	-4,31	-4,53	-4,92	-4,88	-5,11	-5,22	-5,40	-5,67	
	P3.1	-3,07	-5,76	-5,49	-6,34	-6,88	-7,06	-7,06	-6,92	-6,86	-6,89	-6,66	-6,79	-7,07	P3.1	-2,63	-6,28	-5,85	-6,76	-7,34	-7,51	-7,24	-6,98	-6,92	-6,81	-6,57	-6,59	-6,76	
	P4.1	-4,93	-5,08	-5,77	-6,19	-6,51	-6,96	-7,09	-7,26	-7,21	-7,39	-7,61	-7,83	-8,08	P4.1	-4,37	-4,94	-5,40	-5,81	-6,18	-6,75	-6,79	-7,03	-7,02	-7,07	-7,17	-7,32	-7,50	
	P5.1	-0,92	-2,21	-3,14	-4,06	-4,28	-4,30	-4,18	-4,09	-4,38	-4,95	-5,36	-5,78	-6,29	P5.1	-0,36	-2,51	-3,38	-4,35	-4,61	-4,66	-4,33	-4,20	-4,49	-4,91	-5,29	-5,61	-6,00	
	P5.2	-0,77	-2,02	-3,45	-3,93	-3,88	-4,84	-5,24	-5,49	-5,77	-6,05				P5.2	-0,20	-2,31	-3,70	-4,22	-4,19	-5,21	-5,41	-5,58	-5,85	-5,99				
	P6.1	-2,22	-4,01	-4,60	-4,78	-4,76	-5,13	-5,24	-4,83	-4,74	-4,99	-5,19	-5,39	-5,54	P6.1	-1,73	-4,42	-4,92	-5,11	-5,11	-5,51	-5,41	-4,93	-4,85	-4,96	-5,13	-5,23	-5,27	
	P7.1	-1,45	-2,23	-3,01	-3,90	-4,45	-4,06	-4,10	-4,85	-5,10	-5,36	-5,08	-5,03		P7.1	-0,88	-2,19	-2,79	-3,66	-4,24	-3,96	-3,91	-4,74	-5,04	-5,16	-4,77	-4,67		
	P8.1	-2,52		-3,32	-3,93										P8.1	-2,05		-3,56	-4,22										
	P10.1	-1,02	-2,11	-2,79	-2,91	-2,92	-3,63	-4,11	-4,42	-4,43	-4,31	-4,39	-4,71	-5,18	P10.1	-0,47	-2,41	-3,00	-3,15	-3,18	-3,95	-4,26	-4,53	-4,54	-4,29	-4,33	-4,57	-4,92	
P11.1	-2,95				-7,42	-7,46	-7,64							P11.1	-2,39				-7,03	-7,23	-7,32								
P12.1	-1,72	-3,78	-4,03	-3,80	-4,24	-4,66	-4,86	-5,30	-5,69	-6,01	-6,18	-6,32	-6,36	P12.1	-1,21	-4,17	-4,31	-4,09	-4,57	-5,03	-5,01	-5,39	-5,78	-5,95	-6,10	-6,14	-6,07		
P13.1	-2,63	-3,16	-4,50	-4,78	-5,03	-5,42	-5,74	-6,35	-6,61					P13.1	-2,07	-3,09	-4,21	-4,49	-4,78	-5,27	-5,49	-6,16	-6,46						
Mean		-2,1	-3,5	-4,0	-4,4	-5,0	-5,3	-5,5	-5,4	-5,6	-5,7	-5,8	-6,0	-6,4		-1,6	-3,7	-4,1	-4,6	-5,1	-5,5	-5,5	-5,4	-5,6	-5,6	-5,6	-5,7	-6,0	
Median		-2,2	-3,2	-3,8	-4,0	-4,6	-5,0	-5,2	-5,2	-5,5	-5,4	-5,5	-5,8	-6,3		-1,7	-3,1	-4,0	-4,3	-4,7	-5,2	-5,2	-5,3	-5,6	-5,2	-5,3	-5,5	-6,0	
SD		1,2	1,3	1,0	1,0	1,4	1,3	1,2	1,0	1,0	1,0	1,0	1,0	1,0		1,2	1,4	1,0	1,0	1,3	1,2	1,2	0,9	0,9	0,9	1,0	0,9	0,9	
HC	P1.1	-1,57	-1,55	-1,35	-1,39	-1,74	-2,09	-2,07	-1,69						P1.1	-0,99	-0,94	-0,35	-0,16	-0,36	-0,58	-0,55	-0,25						
	P2.1	-2,22	-4,21	-3,83	-3,35	-3,16	-3,02	-3,43	-4,26	-4,77	-5,10	-5,24	-5,39	-5,49	P2.1	-1,76	-3,33	-2,46	-1,82	-1,54	-1,33	-1,64	-2,34	-2,77	-3,04				
	P3.1	-3,30	-3,85	-3,55	-4,26	-4,57	-4,71	-4,50	-4,03	-4,24	-4,35	-4,41	-4,46	-4,50	P3.1	-2,73	-3,31	-2,48	-2,87	-3,01	-3,07	-2,90	-2,58	-2,88	-3,04				
	P4.1	-3,03	-2,93	-2,52	-2,31	-2,38	-2,60	-2,68	-2,85	-3,01	-3,17	-3,32	-3,57	-3,69	P4.1	-2,60	-2,12	-1,30	-0,92	-0,88	-0,97	-0,99	-1,14	-1,29	-1,42				
	P5.1			1,02								-1,74	-1,89	-2,02	P5.1			1,94											
	P5.2								-0,48	-0,62	-0,76				P5.2								0,94	0,74	0,58				
	P6.1													-2,46	P6.1														
	P7.1	-2,63	-2,75	-3,04	-3,00	-2,38	-1,51	-1,43	-1,68	-2,01	-2,25	-2,56	-2,82		P7.1	-2,18	-1,96	-1,77	-1,52	-0,88	-0,03	0,08	-0,15	-0,45	-0,65				
	P8.1	-1,34		-0,42	-0,71										P8.1	-0,76		0,55	0,48										
	P10.1	-0,95	-2,38	-1,60	-1,81	-1,74	-1,69	-1,84	-2,11	-2,12	-2,16	-2,20	-2,15	-2,21	P10.1	-0,36	-1,79	-0,60	-0,56	-0,36	-0,20	-0,33	-0,68	-0,76	-0,83				
	P11.1	-1,82				-3,50	-3,53	-3,60							P11.1	-1,33				-1,84	-1,77	-1,78							
	P12.1									-2,87	-2,69				P12.1									-1,51	-1,36				
	P13.1	-1,66	-1,47	-1,55	-1,35	-1,35	-1,34	-1,52	-1,52						P13.1	-1,16	-0,75	-0,46	-0,10	0,00	0,11	0,01	-0,01						
Mean		-2,1	-2,7	-1,9	-2,3	-2,6	-2,6	-2,6	-2,3	-2,8	-2,9	-3,2	-3,4	-3,4		-1,5	-2,0	-0,8	-0,9	-1,1	-1,0	-1,0	-0,8	-1,3	-1,4				
Median		-1,8	-2,8	-1,6	-2,1	-2,4	-2,3	-2,4	-1,9	-2,9	-2,7	-2,9	-3,2	-3,1		-1,3	-2,0	-0,6	-0,7	-0,9	-0,8	-0,8	-0,5	-1,3	-1,4				
SD		0,8	1,0	1,6	1,2	1,1	1,2	1,1	1,3	1,4	1,4	1,4	1,4	1,4		0,8	1,0	1,4	1,1	1,0	1,1	1,0	1,2	1,3	1,3				
Weight	P1.1	-2,03	-4,02	-4,86	-5,44	-5,74	-5,89	-5,76	-5,64	-5,49					P1.1	-1,65	-4,43	-4,81	-4,99	-5,05	-5,08	-4,97	-4,70	-4,48					
	P2.1	-2,07	-5,02	-6,18	-6,26	-5,72	-5,05	-5,46	-6,25	-6,42	-6,40	-6,17	-6,46	-7,08	P2.1	-1,73	-4,96	-5,48	-5,18	-4,50	-3,92	-4,43	-5,25	-5,33	-5,21	-5,36	-5,55	-6,11	
	P3.1	-2,93	-4,77	-5,40	-6,35	-6,82	-7,26	-7,36	-7,35	-7,61	-7,72	-7,82	-8,90		P3.1	-2,67	-5,31	-5,38	-5,89	-6,07	-6,30	-6,35	-6,07	-6,05	-5,74	-6,23	-7,16		
	P4.1	-3,60	-5,02	-6,64	-7,76	-8,22	-8,41	-8,16	-8,08	-8,09	-8,54	-8,78	-8,64		P4.1	-3,39	-4,96	-5,95	-6,59	-6,78	-6,91	-6,81	-6,78	-6,64	-6,79	-7,50	-7,31		
	P5.1	-1,38	-3,48	-4,18	-4,29	-3,48	-1,46	-0,71	-1,76	-2,80	-3,70	-4,38	-4,53	-5,38	P5.1	-0,96	-3,82	-4,09	-3,86	-2,91	-0,99	-0,41	-1,41	-2,33	-2,92	-3,67	-3,93	-4,65	
	P5.2	-0,74	-2,64	-3,54	-3,99	-4,32	-4,43	-4,66	-4,90	-5,04	-5,49				P5.2	-0,30	-2,88	-3,43	-3,56	-3,71	-3,74	-4,01	-4,10	-4,13	-4,23				
	P6.1	-2,48	-4,39	-5,03	-5,10	-5,09	-5,13	-4,79	-4,79	-4,82	-5,60	-6,00	-5,48	-5,21	P6.1	-2,15	-4,86	-4,99	-4,65	-4,43	-4,39	-4,12	-4,00	-3,96	-4,30	-4,91	-4,67	-4,52	
	P7.1	-3,07	-4,35	-5,30	-5,84	-5,91	-5,21	-4,72	-4,64	-4,61	-4,75	-5,06	-5,50		P7.1	-2,81	-4,25	-4,62	-4,79	-4,68	-4,06	-3,78	-3,88	-3,88	-3,95	-4,43	-4,75		
	P8.1	-1,59		-4,18	-4,45										P8.1	-1,18		-4,09	-4,01										
	P10.1	-1,59	-3,31	-3,85	-3,40	-2,71	-2,49	-2,60	-2,76	-2,96	-3,14	-3,36	-3,85	-4,58	P10.1	-1,18	-3,62	-3,76	-2,99	-2,17	-1,95	-2,16	-2,29	-2,47	-2,49	-2,86	-3,38	-4,02	
	P11.1	-2,82		-5,51	-6,05	-6,73	-7,21	-7,16							P11.1	-2,53		-4,83	-4,98	-5,41	-5,84	-5,93							
	P12.1	-2,70	-4,97	-5,58	-5,79	-5,91	-5,89	-5,76	-5,90	-6,22	-6,05	-5,00			P12.1	-2,41	-5,54	-5,58	-5,34	-5,21	-5,08	-4,97	-4,92	-5,03	-4,62	-4,15			
	P13.1	-2,92	-3,92	-4,99	-5,24	-5,53	-5,37	-5,46	-6,10						P13.1	-2,64	-3,80	-4,32	-4,24	-4,33	-4,20	-4,43	-5,12						
Mean		-2,3	-4,2	-5,0	-5,4	-5,5	-5,3	-5,2	-5,3	-5,4	-5,7	-5,8	-6,2	-5,6		-2,0	-4,4	-4,7	-4,7	-4,6	-4,4	-4,4	-4,4	-4,4	-4,5	-4,9	-5,2	-4,8	
Median		-2,5	-4,3	-5,0	-5,4	-5,7	-5,3	-5,5	-5,6	-5,3	-5,6	-5,5	-5,5	-5,3		-2,1	-4,4	-4,8	-4										

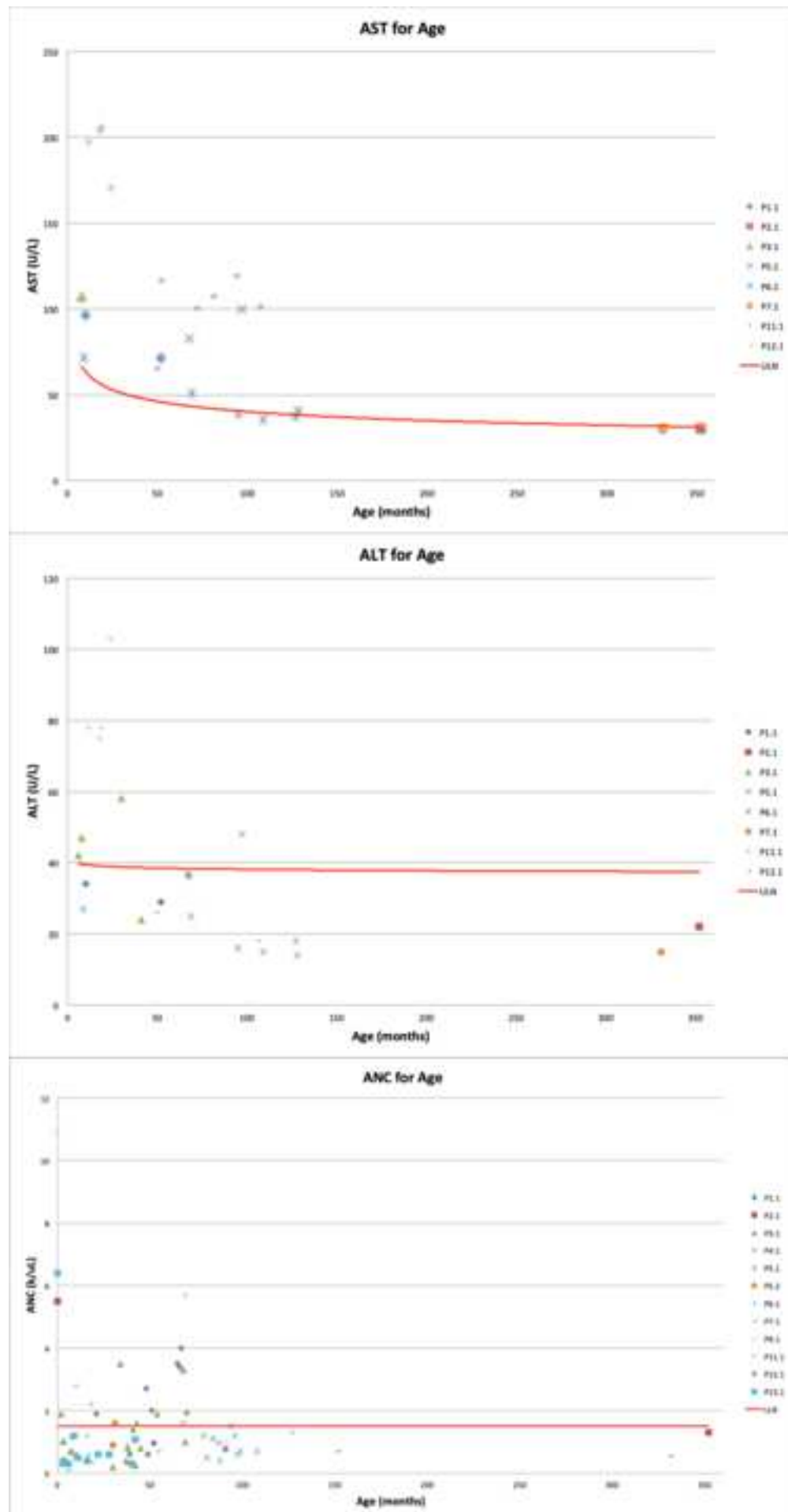














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Corresponding Author Name: Carlos R. Ferreira

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Written informed consent was obtained from all affected individuals or their parents/legal guardians (page 6).
Consent was also obtained for publication of patient photos, where appropriate (page 6).
NCT02450851, NCT02089789, NCT00369421

15. For phase II and III randomized controlled trials, please refer to the [CONSORT statement](#) and submit the CONSORT checklist with your submission.
16. For tumor marker prognostic studies, we recommend that you follow the [REMARK reporting guidelines](#).

## Data deposition

17. Provide accession codes for deposited data. Data deposition in a public repository is recommended for:
  - a. Protein, DNA and RNA sequences
  - b. Macromolecular structures
  - c. Crystallographic data for small molecules
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Deposition is strongly recommended for many other datasets for which structured public repositories exist; more details on our data policy are available in the [Guide to Authors](#). We encourage the provision of other source data in supplementary information or in unstructured repositories such as [Figshare](#) and [Dryad](#). We encourage publication of Data Descriptors (see [Scientific Data](#)) to maximize data reuse.

18. If computer code was used to generate results that are central to the paper's conclusions, include a statement in the Methods section under "**Code availability**" to indicate whether and how the code can be accessed. Include version information as necessary and any restrictions on availability.

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